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The Clinical Diagnosis of Anomalous Pulmonary Venous Drainage

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Clinical studies are presented in: (*a*) One case of partial anomalous pulmonary venous drainage (right common pulmonary vein into inferior vena cava), and (*b*) four cases of total abnormal pulmonary venous drainage (via "left vena cava" and left innominate vein into the superior vena cava on the right side). One of the latter four cases was verified on exploratory thoracotomy. The diagnosis was based on angiocardiography and heart catheterization, but the conventional chest roentgenogram proved to be quite characteristic of both conditions. The relatively slight impairment of health is stressed in the cases reported here.

In the course of the last few years an increasing interest in abnormal venous return has been evident from the literature. Most reports, however, are concerned with anatomic observations unsupported by a complete clinical diagnosis.

For a survey of the anatomic findings the article by Brody[1] may be consulted as well as the more recent review by Chandler Smith.[2] Interesting discussions of the embryologic consideration related to anomalies of the pulmonary veins may be found in the articles of Edwards and his associates.[3, 4] According to Chandler Smith there are now 133 cases on record, 75 with partial and 56 with complete drainage of the pulmonary venous blood into the right atrium or its tributaries. The latter group can be subdivided in accordance with the findings of Brody into 23 cases with and 33 cases without additional cardiac abnormalities. In all cases of total abnormal drainage, however, where mention has been made of the foramen ovale, this was found to be open; the additional cases cited by Chandler Smith all show the same feature.

The usual sites into which the pulmonary veins emptied in cases of partial abnormal drainage were found to be: superior vena (35 cases), right atrium (18 cases), and left innominate vein (16 cases). Drainage into the coronary sinus, inferior vena cava, azygos vein and left subclavian vein was seen less frequently. In cases of total anomalous pulmonary venous return the structures into which the pulmonary veins entered were the following: superior vena cava (nine cases), coronary sinus (seven cases), right atrium (six cases), left innominate vein (three cases) and portal vein (two cases).

Most of the patients with partial abnormal drainage maintained good health until an advanced age, their life span varying from 1 to 86 years. On the other hand total abnormal drainage without other major cardiac defects was tolerated notably less well, only 5 out of 33 patients lived beyond the age of 8 months. The same trend applied when complete abnor-

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From the Center of Cardiological Studies, University Hospital, Leiden and the Department of Pediatrics, Zuiderziekenhuis, Rotterdam. Investigations in cases 1, 2, 3 and 4 were carried out with the cooperation of Drs. P. J. van Kuyk (Department of Roentgenology), C. Bruins (Department of Pediatrics), F. J. van Dam, J. A. Smits, H. G. Verdonk, Th. W. van Wijk, G. B. A. Schasfoort and F. A. Rodrigo M. S. (Department of Cardiology).

mal return was associated with additional anomalies; in this group 5 out of 23 patients lived longer than 8 months.[2] In three cases of complete abnormal pulmonary venous drainage, recently studied post mortem in the department of anatomy of our University, the pulmonary veins were found to empty into the coronary sinus (one case) and into a persistent sinus venosus associated with a persistent left vena cava (two cases). These anatomic findings and their embryologic significance will be discussed in another publication.

In this paper we propose to deal with one case of partial abnormal drainage (right pulmonary vein into the inferior vena cava) and four cases of complete abnormal pulmonary venous return (into left innominate vein), all of which were diagnosed clinically.*

Method of Examination

Heart catheterization was carried out by the accepted procedure. In case 2, only mean pressures were taken by means of a saline manometer. In case 1, pressures were registered optically with a Hamilton-type manometer constructed by Prof. Dirken, and a simultaneous electrocardiogram was made with a Boulitte string galvanometer. In cases 3 and 4 pressure registration was effected through a Statham gage connected to a six-channel Elmquist electrocardiograph by a suitably constructed amplifier; the electrocardiogram and respiration curves were registered together with the blood pressure curves.

The oxygen saturation of blood samples was determined photoelectrically, in cases 1, 3 and 4 with the hemoreflectometer of Brinkman[5]; in case 2, with the older apparatus of Brinkman, using absorption of light instead of reflection as index. As will be seen from tables 1, 3 and 4 we have sometimes taken many blood samples (even more than were listed because some merely corroborative figures were omitted). This was greatly facilitated by the use of the hemoreflectometer, which provides a quick and simple method of determining oxygen saturation with sufficient accuracy, the mean difference in saturation found in duplicate samples from the same syringe not exceeding 1 per cent. For calculating cardiac output, however, one has to determine oxygen capacity by the Van Slyke method or calculate this value from an accurate hemoglobin estimation. For the latter purpose we now use the alkaline hematin method checked by blood iron determination.

For angiocardiography Diodrast 70 per cent or Diodrast 80 per cent was used, the substance being injected either intravenously or through a heart catheter. A simple cassette changer was used which allowed a succession of roentgenograms at time intervals of one to two seconds.

Description of Cases

Case 1. G. B., a 21 year old woman, was examined in November, 1950. The patient had been free of symptoms until three years before examination when, after her father's death, she was obliged to do fairly strenuous work. She then began to complain of breathlessness and of pains in the chest and in the lower back. She was never blue.

On examination no cyanosis or clubbing was noted. There were no signs of heart failure. The chest was symmetric; respiratory movements were equal on both sides. At the left and right sternal border in the third intercostal space a grade 2 systolic murmur was heard and a very faint thrill was felt. No diastolic murmur was heard. Blood pressure was 135/80. Urine examination was negative. Hemoglobin was 12.5 Gm. and hematocrit 40 per cent. White blood corpuscles were 7600 with normal differential count. The arterial oxygen saturation was normal (97 per cent). Circulation time was eight seconds (with magnesium sulphate). The electrocardiogram showed doubtful disturbances in the form of widened and notched S waves in leads II, III and V_F.

On roentgenologic examination the heart seemed to be rotated to the right and upward; on placing the patient in a slightly oblique position (right anterior oblique) a reasonably normal configuration was obtained. The right atrium appeared to be enlarged. The main pulmonary artery and its hilar branches were not conspicuously wide; no increased pulsations were visible. Parallel to the right lower cardiac border, and at a short distance from it, a rather broad abnormal vascular shadow was to be seen which disappeared under the diaphragm and which gave the appearance of a branching effect into the upper lung field (fig. 1*A*). On a planigraphic film the vascular nature of this shadow was more marked, and the branches reaching high in the thorax were better seen (fig. 1*B*).

On the intravenous angiocardiogram the same shadow was outlined at the moment the pulmonary veins were supposed to fill and the extension of the former into the region of the inferior vena cava was seen. At a later date a heart catheter was passed through the saphenous vein into the inferior vena cava just below the diaphragm. Although the connection of the abnormal pulmonary vein with the inferior cava could be established by passing the

* In every case the diagnosis could be made by heart catheterization and in three cases by angiocardiography; in one case the diagnosis was confirmed at exploratory thoracotomy. The conventional chest roentgenogram also proved to be quite characteristic.

tip of catheter into the former, the anomalous vessel did not fill immediately after injection of Diodrast through the catheter but only after filling of the right heart and the pulmonary artery and simultaneously with a left pulmonary vein. It remained visible from four to eight seconds after injection (fig. 1*C*). It was felt, that the shadow represented a pulmonary vein draining the right lower lobe and, considering that it reached high up in the lung field while still fairly wide, probably the

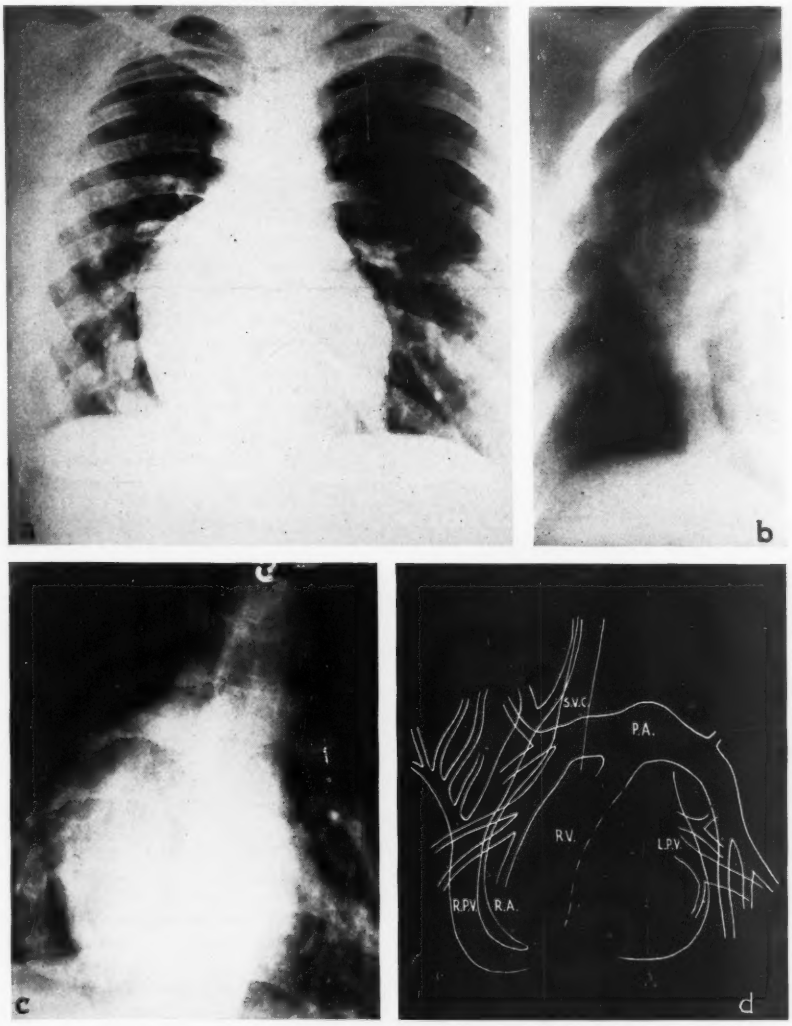

FIG. 1. Anteroposterior view of case 1: (*a*) Chest roentgenogram. Anomalous pulmonary vein visible parallel to the right border of the heart. (*b*) Planigraphic film (6 cm. from the back). Branching of anomalous pulmonary vein extending into the upper thorax. (*c*) Angiocardiogram five seconds after injection of Diodrast. Filling of anomalous pulmonary vein, which turns to the left at the junction of inferior vena cava and right auricle. (*d*) Diagram combining the findings of the planigraphic and angiocardiographic films.

S.V.C. = superior vena cava
P.A. = pulmonary artery
R.P.V. = right (common) pulmonary vein.
R.V. = right ventricle
R.A. = right auricle
L.P.V. = left pulmonary vein(s).

other right lobes as well. There was no early filling of the left heart or aorta, that is a right to left shunt was not demonstrated. The left ventricle and aorta were not visible until the shadow of the pulmonary veins had already begun to fade.

TABLE 1.—*Case 1*

Tip of catheter in:	O_2 Saturation (%)	Syst./Diast. Pressure (mm. Hg)	Mean Pressure (mm. Hg)
Heart catheterization: Nov. 28, 1950			
Superior vena cava	65		10
Right atrium	78		15
Right ventricle, outflow tract	80	±50/20	
Right pulmonary artery, central part	81	40/25	
Right pulmonary artery, central part	83	40/20	
Right brachial artery	97	135/80	
Heart catheterization: Dec. 12, 1950			
Inferior vena cava, 4–5 cm. below the diaphragm	82		
Inferior vena cava, 3–4 cm. below the diaphragm	84		
Inferior vena cava, near level diaphragm	80		
Inferior vena cava, 1 cm. above diaphragm	97		
Pulm. vein entering inferior vena cava	97		5
Right atrium, center	96		6
Right atrium, near center	81		
Right atrium, near A-V valves	88		
Right atrium, near S.V.C.	67		
Sup. vena cava	65		
Right ventricle, inflow tract	81	30/−3	
Systemic flow/min./M^2 = 4.1 L.			
Pulmonary artery flow/min./M^2 = 6 L.			
Efficient pulmonary flow/min./M^2 = 4.1 L.			

The oxygen saturations of various blood samples obtained by heart catheterization are listed in table 1, which also gives the pressures measured. Catheterization of the right ventricle and pulmonary artery was made difficult by repeated runs of ventricular extrasystoles, associated with nervousness and a sense of oppression and had to be cut short.

Conclusion. There was drainage of a right common (?) pulmonary vein into the inferior vena cava at a point near its entrance into the right atrium. No certainty concerning the existence of an atrial septal defect or the cause of the systolic murmur (originating in the abnormal pulmonary vein or caused by an open foramen ovale?) was obtained. The abnormal pulmonary vein was demonstrated by angiocardiography, but was visible on a conventional x-ray film of the chest and was even more clearly seen on planigraphic sections at a distance of 5 to 7 cm. from the back.

The patient was seen again in November, 1951; as long as she did only light work she was symptom free. The clinical and roentgenologic findings were unchanged.

Case 2. A. L., a boy of 7 years was examined in July, 1948. At birth the patient was found to have a cardiac defect and he was cyanotic during the first few days of his life. After that time intermittent cyanosis occurred, particularly during bouts of fever, and on effort. He has always tired easily and been short of breath. He has a frequent, slight, unproductive cough. He has never had pneumonia. His hands and feet are always cold.

During rest only a very slight degree of cyanosis was seen; clubbing of fingers and toes was equally slight. There was some bulging of the precordial chest area. A moderately loud systolic murmur (grade 3) was heard at the lower left sternal border, where a systolic thrill was also felt. No diastolic murmurs were audible. The femoral arteries were found to pulsate normally. The lungs were clear. The liver was found to be placed in the left hypochondrium; the stomach on the right side. Blood pressure was 80/55. Urine examination was normal. Hemoglobin was 16.4 Gm. Erythrocytes numbered 5,150,000. The electrocardiogram showed pronounced right axis deviation in standard leads. The records of the precordial leads have been mislaid, unfortunately, and are missing.

On roentgenologic examinations the heart was found to be moderately enlarged, more so to the left than to the right. In the left oblique view the enlargement seemed chiefly confined to the right ventricle. The right atrium was dilated; the left atrium appeared normal. On both sides of the upper mediastinum a large rounded shadow was seen to bulge into the lung fields; the right shadow was more prominent than the left. Both shadows pulsated, but not vigorously. With the heart shadow they formed a figure-8 shaped mass (fig. 2*A*).

Through the left paramediastinal shadow a widened pulmonary artery was seen; the hilar branches and peripheral lung vessels were also more conspicuous than normal. The aorta was not clearly seen; the esophagus did not show an impression of the aortic knob.

After in intravenous injection of Diodrast the right upper paramediastinal shadow began to fill immediately and revealed itself to be the superior vena cava (fig. 2*B*). Two seconds later the pulmonary artery with its branches filled and these were seen to be widened. The aorta filled at the same time and appeared to be definitely smaller than the pulmonary artery (fig. 2*C*). Two seconds later (four and one half seconds after injection) the pulmonary artery and aorta were no longer visible, but the left upper mass was filled and a wide arch was seen connecting the left hilar region with the superior vena cava (fig. 2*D*). Six and one half seconds after injection the density of this arch became less, but that of the pulmonary artery increased. After two additional seconds the venous arch was again more

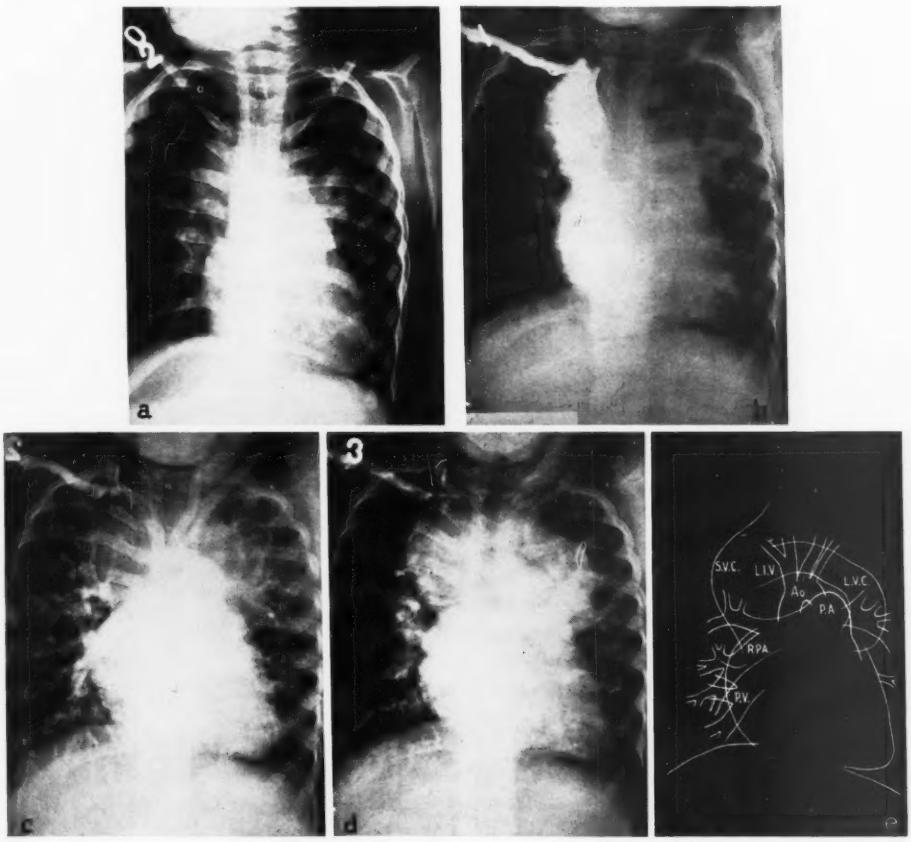

FIG. 2. Anteroposterior view of case 2: (*a*) Before injection of Diodrast. (*b*) One-half second after injection. Filling of superior vena cava and right auricle. (*c*) Two and one-half seconds after injection. Filling of right and left heart, aorta and pulmonary artery. (*d*) Four and one-half seconds after injection. Filling of "left vena cava" with renewed filling of right superior vena cava and right auricle. (*e*) Diagram combining the findings of the angiocardiographic films.

S.V.C. = superior vena cava
L.V.C. = "left vena cava"
L.I.V. = left innominate vein
R.P.A. = right branch of pulmonary artery.
P.A. = pulmonary artery
Ao = aorta
P.V. = pulmonary vein.

clearly visible, demonstrating a recirculation through the lungs.

On catheterization the oxygen saturation in samples taken simultaneously from the root of the superior vena cava and the femoral artery were found to be nearly equal (table 2). The mean pressure in the pulmonary artery was found to be very much increased, though disproportionately when compared with the pressure in the right ventricle. This was felt to be due to restlessness of the child; the discrepancy between the oxygen saturation in the right ventricle and in the pulmonary artery compared with the saturation in the femoral artery is most probably to be explained in the same way. Repetition of the catheterization was not possible.

TABLE 2.—*Case 2*

Tip of catheter in:	O_2 Saturation (%)	Mean Pressure (cm. H_2O)
Left subcl. vein	69	
Sup. vena cava, high at the entrance of left innom. vein	85*	
Sup. vena cava, half way	76	
Sup. vena cava, half way	74	
Right atrium		8–9
Right ventricle, center	77	29
Right ventricle, center	69	31.5
Right pulm. art., central part	68	104
Femoral artery	86*	
Femoral artery	87†	

* Samples taken simultaneously.

† Second sample from femoral artery taken immediately after first sample.

Conclusion. Total drainage of pulmonary blood into the superior vena cava by way of a left vertical vein ("left vena cava") and the left innominate vein was considered highly probable; an Eisenmenger syndrome was also thought to be present, especially in view of the high pulmonary artery pressure. The possibility of a virtually simultaneous filling of aorta and pulmonary artery via an atrial septal defect could not be excluded, however; the aorta seemed to be too narrow for an Eisenmenger complex. Situs inversus abdominis was also found.

Case 3. J. F. la P., a young man of 20 years, was examined in May, 1951. Palpitation and dyspnea on exertion have occurred since childhood. The patient shows cyanosis in cold weather, coughs frequently without expectoration. At a young age he suffered from asthmatic bronchitis for several years and has also had bronchopneumonia once. On examination the patient appeared slightly cyanotic. No clubbing was present. In the aortic area a superficial and rather soft continuous murmur was heard. This resembled a venous hum, but was not influenced by altering the position of the head. The second pulmonic sound was loud and reduplicated. At the lower left sternal border a systolic murmur, grade 3, accompanied by a thrill was present. The femoral arteries showed normal pulsations. The edge of the spleen could just be felt. Blood pressure was 120/75 in both arms.

Hemoglobin was 14.7 Gm.; erythrocytes 4,660,000; hematocrit 48. The white blood cell count and differential were normal. The sedimentation rate was 2 mm. after one hour and 5 mm. after two hours. Urine was negative except for a positive urobilin test. Circulation time was 22 seconds with magnesium sulfate. The arterial oxygen saturation at rest was 88; after exercise 80. The electrocardiogram was interpreted to show right heart strain.

On roentgenologic examination the heart was found to be slightly enlarged; in the left oblique position the enlargement appeared to be restricted to the right ventricle and atrium. The same saccular bulging of both sides of the upper mediastinum which was present in case 2 was also present in case 3 (fig. 3). The right paramediastinal shadow was more intense than the left and both showed faint pulsations. A wide pulmonary artery was seen through the left shadow. The aorta was barely visible and was small. The pulmonary hilar branches were widened and pulsated freely.

Angiocardiography was carried out anteroposteriorly with intravenous injection of 80 per cent Diodone. The superior vena cava (right upper paramediastinal shadow) was seen to fill first. This was followed successively by filling of the right ventricle and pulmonary artery. The "left vena cava" (left upper paramediastinal shadow) filled after two or three more seconds and renewed filling of the superior vena cava on the right side followed. The aorta was not clearly seen. Marked dilution of the radio-opaque substance occurred apparently in the wide (right) superior vena cava. Oxygen saturation values obtained through heart catheterization and the measured pressures are listed in table 3. There was an admixture of highly oxygenated blood in the superior vena cava with the result that all saturation values in the right atrium, right ventricle and pulmonary artery were found to be at about the same high level. This probably precluded the detection of a septal defect through demonstration of a rise in saturation of the blood. From comparison of the pressures found in the inflow and outflow tract of the right ventricle, the presence of an infundibular stenosis could be diagnosed. The localization of the ventricular site, where the pressure gradient was found, was established at fluoroscopy during catheterization.

Conclusion. It is probable that all the pulmonary veins drained into a left vertical vein ("left vena cava") which emptied into the left innominate vein, and by way of this vessel into the superior vena cava on the right side. Probable infundibular stenosis of the right ventricle, and possible atrial septal defect in addition was present. The presence of the latter is suggested by the murmur and thrill at the left lower sternal border and the constant finding of this anomaly in cases with a completely abnormal pulmonary venous return. On the chest film no indication of a pulmonary stenosis had been seen; the heart size was only slightly increased. It seems possible that the high ventricular pressure due to the infundibular stenosis may have been an advantage in this case in that it better directed the blood from the right side of the heart to the left.*

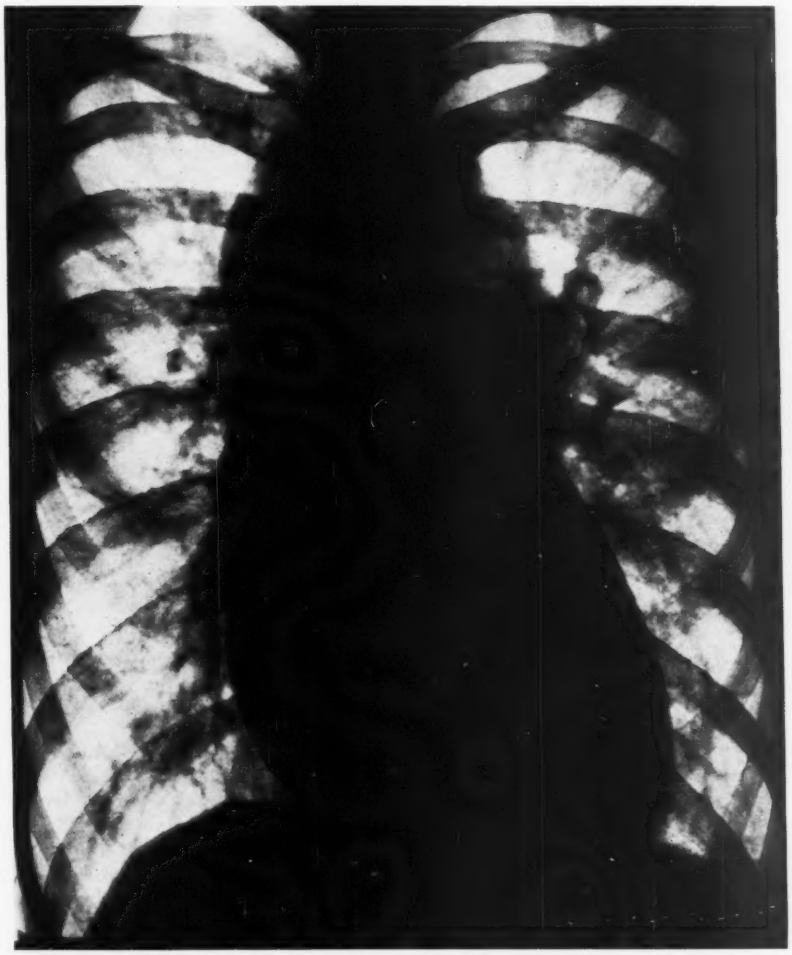

FIG. 3. Anteroposterior view of chest in case 3.

Case 4. K. M., a 22 year old woman, was examined in June, 1951. The patient gave a history of having been easily exhausted and breathless since childhood. When examined her condition was somewhat better than it had been earlier; however, she could

* This point was brought out by Dr. Helen Taussig in reviewing this paper.

not do heavy house work. According to her mother her lips were cyanotic when she became exhausted. There was no cough and no predisposition to respiratory infections. She was mentally slow.

On examination no cyanosis was exhibited during rest, but slight clubbing of the fingers was present.

TABLE 3.—*Case 3*

Tip of catheter in:	O_2 Saturation (%)	Syst./ Diast. Pressure (mm. Hg)	Mean Pressure (mm. Hg)
Left subclavian vein	63		
Sup. vena cava, right, high in S.V.C.	95		0
Sup. vena cava, right, half way in S.V.C.	93		
Sup. vena cava, right, low in S.V.C.	92		0
Inf. vena cava	73		3
Right atrium, high (near S.V.C.)	92		2
Right atrium, middle	87		0
Right atrium, middle	81		
Right atrium, near A-V valves	86		0
Right ventricle, near A-V valves	85	110/0	
Right ventricle, middle		105/0	38
Right ventricle, outflow		58/0	18
Right ventricle, outflow	91	55/0	
Right pulm. artery, central	89*	55/10	34
Right pulm. artery, central		55/15	30
Right pulm. artery, more peripheral	87	55/20	
Right pulm. artery, "capillary"	93		12
Left brachial artery	89*	128/68	82
Left brachial artery, second puncture	85		
Left brachial artery, after exercise on table	77		
Systemic flow/min./M^2 = 3.8 L.			
Pulmonary flow/min./M^2 = 8 L.			
Efficient pulmonary flow/min./ M^2 = 2.8 L.			

* Samples taken simultaneously.

On auscultation a superficial, soft, continuous murmur ("venous hum") was heard over the aortic area. This was the same type of murmur that was present in case 3. A grade 3 systolic murmur, maximal in the third and fourth intercostal spaces at the lower left sternal border and accompanied by a thrill, was present. In the lungs and the abdomen nothing abnormal was found. Pulsations of femoral and pedal arteries were well marked. There were no signs of heart failure. Blood pressure was 125/80 in the right, 115/70 in the left arm. Arm to tongue circulation time was 13 seconds with Decholin and 12 seconds with fluorescein.

Hemoglobin was 14.4 Gm. Erythrocytes 4,400,000. The white blood cell count and differential were normal. Urine examination was negative. Meinicke blood reaction was negative. Erythrocyte sedimentation rate was 1 mm. after one hour and 2 mm. after two hours. Blood urea nitrogen was 44 mg. per 100 cc. Arterial oxygen saturation at rest was 90 and after exertion (two-step test) 83. The electrocardiogram was interpreted to show right heart strain with incomplete right bundle branch block.

On roentgenologic examination of the thorax, the upper mediastinum showed saccular bulgings on both sides that were similar to those present in cases 2 and 3. These caused a figure-8 shaped shadow, the heart forming the lower half of the 8 (fig. 4*A*). The right upper shadow was more prominent than the left and its pulsations were also more marked. Through the left shadow the widened pulmonary artery was seen, and this showed vigorous pulsations. The hilar vessels were wide and also freely pulsating. The vessels in the periphery of the lung were found to be unusually dense. The aortic knob was not seen. The heart itself was slightly enlarged in the left oblique position. The enlargement appeared to be confined to the right atrium and ventricle.

Angiocardiographic examination yielded the following findings:

1. In the anteroposterior view after the intravenous injection of Diodone the right upper paramediastinal shadow (superior vena cava) was seen to fill immediately following the injection and at the same time small veins in the regions of the mediastinum and thoracic inlet became visible (backflow of Diodone due to congestion). After one second the right heart and pulmonary artery began to fill, followed after one and one-half to three seconds by the visualization of a small aortic knob. Five and one-half seconds after injection the left upper paramediastinal shadow was filled and had the shape of a curved tube, the end of which appeared to be connected to the superior vena cava.

2. In the anteroposterior view after injection of Diodone through a catheter lying with its tip in the main pulmonary artery, essentially the same findings as recorded under 1 were noted.

3. In the anteroposterior view after injection of Diodone through a catheter the tip of which is placed in the right pulmonary artery (peripheral to the right lower lobe) arterial branches were filled immediately (fig. 4*B*) and within one half second a gradually increasing filling of widely patent con-

verging veins was seen to take place. The lower and wider vein could be followed through the heart shadow to the left border of the vertebral column, too far to the left to have a normal entrance into the left atrium (fig. 4*C*). After a few seconds the occurrence of a faint opacification of the "left vena cava" was noted.

4. In the left oblique view after the intravenous injection of Diodone, partial filling of the superior vena cava, lying anteriorly in this position, was seen to have taken place after one second. From this film it was evident that on fluoroscopy the ascending aorta in this case as in the others (cases 2, 4 and 5) was obscured by the shadow of the superior vena cava in the left oblique position. Two and one-half seconds after injection the right and left heart filled, thus demonstrating a septal defect. At four seconds after injection the pulmonary veins began to fill and a faint shadow of Diodone in the "left vena cava" was seen, this was very distinct from five and

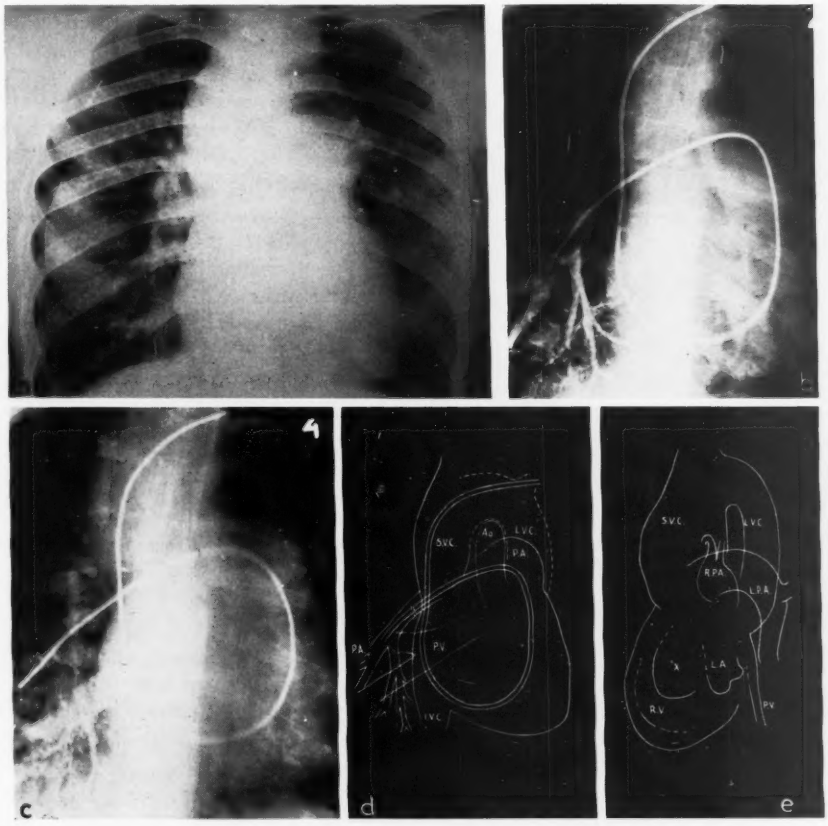

FIG. 4. Roentgenologic findings in case 4: (*a*) Anteroposterior view of chest. (*b*) A–P view two seconds after injection of Diodrast: catheter in right lower lung field. Arterial filling. (*c*) Same view three seconds later. Filling of right pulmonary vein, which crosses over to the left of the vertebral column. (*d*) Diagram of findings in figures 3*a* and 3*b*, combined with those of the films made after intravenous injection (not reproduced). (*e*) Diagram of findings in angiocardiographic films in the left oblique view after intravenous injection (not reproduced).

S.V.C. = superior vena cava
L.V.C. = "left vena cava"
R.P.A. = right branch of pulmonary artery.
L.P.A. = left branch of pulmonary artery.
P.V. = pulmonary vein
I.V.C. = inferior vena cava
Ao = aorta
X = central part of right atrium (filled throughout during later stages of angiocardiographic series).
L.A. = left atrium.

TABLE 4.—*Case 4*

Tip of catheter in:	O_2 Saturation (%)	Syst./Diast. Pressure (mm. Hg)	Mean Pressure (mm. Hg)
Heart catheterization: June 4, 1951			
Left subclavian vein	78		
Left anonymous vein	97		
Sup. vena cava, high (at root)	98		0
Sup vena cava, half way	97		
Sup. vena cava, at entrance R atrium	96		−3
Inf. vena cava, 3 cm. under diaphragm	73		−2
Right atrium, near S.V.C.	96		
Right atrium, center	94		−3
Right atrium, near A-V valves	93		−2
Right ventricle, center	91	50/−1	
Right ventricle, outflow tract		±40/−2	14
Right pulm. art., central	94	±25/14	
Right pulm. art., central	93	28/15	19
Right pulm. art., "capillary"			8
Right femoral artery	93	110/70	82
Heart catheterization: June 11, 1951			
"Left vena cava"	97		
Sup. vena cava, tip rotated upwards above entrance left inominate vein	76		
Sup. vena cava, tip rotated upwards above entrance left innominate vein	67		
Sup. vena cava, high but below entrance left innom. vein	92		0
Sup vena cava, half way	95		2
Right atrium, near entrance inf. V.C.			0
Right ventricle, central	93	45/0	19
Right pulm. art., central	91	28/12	
Systemic flow/min./M^2 = 4.5 L.			
Pulmonary artery flow/min./M^2 = 19 L.			
Efficient pulmonary flow/min./M^2 = 4 L.			

one-half seconds onwards. The wide connection of the point of confluence of the pulmonary veins to the origin of the vertical "left vena cava" was also seen (fig. 4*C*). In a late stage (7 to 10 seconds after injection) the atrial septum itself appeared to show a high defect.

The findings on two heart catheterizations are given in table 4.

Conclusion. There was drainage of all pulmonary veins into the (right) superior vena cava through a "left vena cava" and the left innominate vein, a probable atrial septal defect with a virtually simultaneous filling of the aorta and pulmonary artery, and a greatly increased pulmonary flow with normal pressure in the pulmonary artery.

The pressure curves show some elevation of systolic pressure in the right ventricle over the pulmonary artery, but owing to disturbances in the curves caused by vibrations in the catheter, the exact height of the pressure gradient is difficult to compute, although in any event this is not great. On the other hand it is conceivable that a definite, though slight, pressure gradient between right ventricle and pulmonary artery may be due to an abnormally increased flow through normal pulmonary valves, which thus show a degree of relative stenosis.

The value given in table 4 for pulmonary flow is excessively high (19 liters per minute per square meter of body surface). It should be kept in mind, however, that in this case as in the other cases of total anomalous pulmonary drainage the difference in oxygen saturation between the pulmonary artery and the systemic arteries is very small. The calculation of pulmonary artery flow from the Fick formula is correspondingly inaccurate.

Case 5. R. L. a 5 year old boy, was examined in May, 1950 and in February, 1951.* The birth was normal. Feeding during the first year was rather difficult; gain in weight was slow, the baby weighing only 5000 Gm. at the end of the first year. The patient commenced walking at the age of 3 years, although the efforts made were poor and he has been able to continue the effort for only an hour at a time. The history which we obtained indicated that he still coughs and becomes dyspneic after

* The investigations in this case were carried out in the Zuiderziekenhuis of Rotterdam, in all other cases in the University Hospital at Leyden.

exertion and that he suffers from frequent attacks of bronchitis.

On examination the patient was found to be backward in physical development (height 1.03 meters, weight 16 Kg.), slightly cyanotic and to have a leftsided chest deformity. A definite systolic murmur was heard over the whole cardiac area and was most pronounced in the second intercostal space at the left side of the sternum. The second pulmonary sound was very loud. The heart rate at rest was 100 beats per minute. In the erect position visible pulsations in the veins of the neck were seen. The pulsations of the femoral artery were palpable. The liver and spleen were enlarged. No abnormal findings were discovered in the examination of the lungs; blood pressure was 110/80.

Hemoglobin was 13 Gm. Erythrocytes numbered 5,600,000 per cubic millimeter. Nothing was found on urinalyses except a slightly positive test for urobilinogen. Arterial oxygen saturation at rest was 81 to 85 per cent.

The electrocardiogram showed incomplete right bundle branch block.

On roentgenologic examination the heart was found to be greatly enlarged; study in the left oblique position showed this to be due particularly to the right ventricle. The pulmonary conus of the right ventricle was abnormally full, probably due to a dilated pulmonary artery. The aortic knob appeared to be underdeveloped. On both sides of the upper mediastinum weakly pulsating shadows were visible. These ran symmetrically on both sides of the spine and bulged laterally, the shadow on the right being the more pronounced of the two (fig. 5).

Table 5 shows the oxygen saturation and pressures found on heart catheterization in May and February, 1951. The superior vena cava sample had a saturation of 87 per cent and this was much higher than the saturation in samples from the inferior vena cava. It was possible to pass the catheter through the innominate vein into the left superior vena cava, where blood with a saturation of 96 per cent was found. The catheter passed very easily through an open foramen ovale. The oxygen saturation in the left atrium was below normal, probably because of a right to left shunt through the foramen ovale. In the right atrium, right ventricle and pulmonary artery, the oxygen saturations were at about the same level. The systolic pressures in the right ventricle and pulmonary artery were distinctly elevated. Because of the connection between the two superior "venae cavae," much of the highly oxygen-saturated blood passed through the right side of the heart and recirculated through the lungs, thereby resulting in an overburdening of the pulmonary circulation.

It was thought at first that the left atrium probably also received oxygenated blood from other veins of the lungs and it was decided to undertake an exploratory thoracotomy and, if possible, to disconnect the superior venae cavae from each other. Dr. P. J. Kooreman performed the operation Oct. 4, 1951. His report follows.

"After opening the left thorax by resection of the fourth rib, a vessel as large as a thumb became visible. The wall of this structure resembled a vein. This vessel seemed to run from the base of the heart upwards into the neck. The aorta was small; the pulmonary artery very distended. The large vessel

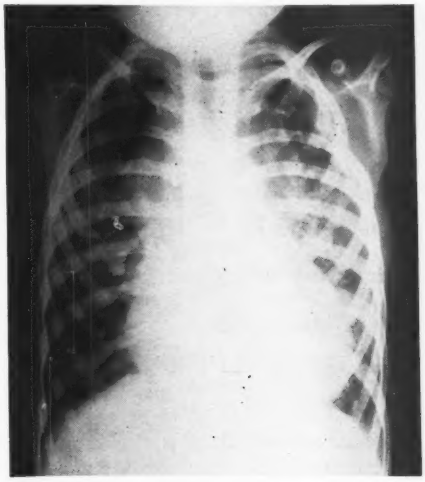

FIG. 5. Anteroposterior view of chest in case 5.

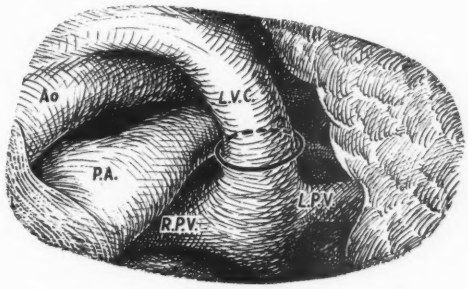

FIG. 6. Anatomic findings at thoracotomy in case 5 (see text).

mentioned above lay free in its surroundings and it was possible to pass behind it. In its upper part this vessel appeared to turn to the right. In its lower part the vessel received the left superior pulmonary vein. Below the entrance of this vein the vessel appeared to turn to the right (toward the right auricle?). This vessel was ligated above the entrance of the superior pulmonary vein. Very shortly after this procedure the heart almost stopped beating. On quickly removing the ligature heart function became normal again. A second closure of the vessel

with a soft clamp, again produced the same effect. Further attempts to close the vessel were abandoned and the thorax closed." (See fig. 6.)

Conclusion. From the experience gained we came to the conclusion that probably all the pulmonary veins from both lungs drained into a large vessel which we shall call a left superior vena cava. This vessel had no connection at all with the left auricle, but conducted all its blood via an innominate vein into the right superior vena cava.

TABLE 5.—*Case 5*

Tip of catheter in:	O_2 Saturation (%)		Systol./Diast. Pressure (mm. Hg)		Mean Pressure (mm. Hg)	
	I*	II	I	II	I	II
Sup. vena cava, right, high (lateral)	84	83			7	6
Sup. vena cava, halfway (lateral)	85	85			6	8
Sup. vena cava, halfway (medial)	94	87			10	8
Sup. vena cava, low (medial)		87				8
Sup. vena cava, left, photo	96				10	
Inf. vena cava	76					
Right atrium	87	85			5	7
Right ventricle	85	83	68/9	84/10		
Pulm. artery	87		60/11			
Pulm. artery	87					
Left atrium	90	82			8	9
Femoral artery		81				
Systemic flow/min. = 4 L. Pulmonary artery flow/min = 7.3 L.						

* The numbers I and II correspond with the first and second catheterization of the heart.

DISCUSSION

It can be seen from the description of our cases that at least in one pattern of partial anomalous, pulmonary venous drainage and in one pattern of complete anomalous return of pulmonary veins, a clinical diagnosis can be made on the conventional chest roentgenogram, while confirmatory evidence may be obtained from both heart catheterization and angiocardiography. The two patterns are: (*a*) inflow of a common right pulmonary vein into the inferior vena cava, and (*b*) drainage of all pulmonary veins into a left vertical vein which empties into the superior vena cava through the left innominate vein. The left vertical vein has been called "left vena cava" throughout this communication; the question of whether one is entitled to give this name to a vein, which in all probability does not communicate with the coronary sinus, will be discussed in a later article.

Partial Abnormal Pulmonary Venous Drainage. The pattern of partial anomalous drainage described above seems to be identical with the arrangement of the pulmonary veins in the two patients described by Dotter, Hendisty and Steinberg.[6] Both patients were men, aged 27 and 41 years, respectively. The anomaly was discovered more or less accidentally since the patients were symptom free.

Three other closely similar cases have been reported by Grisham, Poppel, Simpson and Sussman.[7] The three patients were men of 24, 22 and 26 years, respectively. In one patient systolic and diastolic murmurs over the pulmonary area and to the right of the lower part of the sternum were heard; in the two other patients only a systolic murmur over the pulmonary area was audible. All three were reported to have electrocardiograms showing incomplete right bundle branch block. One case was discovered on a routine roentgenographic examination of the chest, the others were known to have had cardiac murmurs from early childhood.

The diagnosis of atrial septal defect associated with an aberrant right lower lobe pulmonary vein, made by Grishman and his co-workers in their cases, was based on the roentgenologic findings, in particular on serial angiocardiograms. Although Grishman,[7] Brahms, Gordon and King[8] in another article apparently describe more fully one of the cases of Grishman, Poppel, Simpson and Sussman, adding some oxygen values obtained by heart catheterization, it still remains doubtful, in our opinion, whether their case is identical with ours in respect to the territory drained by the aberrant vein. Because of the roentgenograms

which show the aberrant right pulmonary vein extending high in the chest, and because of the apparently large flow through it, we feel that at least in our case the anomalous vein was draining the whole of the right lung.*

The diagnosis made by Grishman and his associates was made by Dotter and his co-workers.

The associated septal defect was not conclusively demonstrated in our case. It may be remarked in passing that we have felt recently on considering the possibility of aberrant veins, that the diagnosis of uncomplicated atrial septal defect would seem doubtful in some of our earlier cases, since this diagnosis was based solely on oxygen saturation differences, and was not unequivocally demonstrated either in the angiocardiogram, or by pushing the catheter through the defect into the left atrium.

It is not to be inferred that the pattern of partial anomalous pulmonary venous drainage described above is the only type which lends itself to clinical diagnosis, although as far as we have been able to ascertain, it is the only one that is diagnosed roentgenologically at this moment. Many observers,[9, 10] including ourselves, have encountered on heart catheterization isolated or sometimes multiple pulmonary veins draining into the superior or inferior vena cava, or into the right atrium.

Here again caution should be exercised in the diagnosis, unless the catheter is seen to pass directly from the right atrium, or from either vena cava, directly in the pulmonary vein. Aberrant pulmonary veins have also been seen during thoracotomy.[11] So far all available evidence seems to prove that clinically and anatomically partial drainage of the pulmonary veins into the superior vena cava and right atrium is observed most commonly; drainage into the inferior vena cava seems to have been encountered more frequently in clinical practice than at autopsy.

The clinical significance of partial anomalous pulmonary venous drainage is not apparently very great, most cases being discovered more or less accidentally on routine examinations during thoracotomy for other purposes, or in the course of the investigation of other associated anomalies which dominated the clinical picture. According to Brody[1] and Hughes and Rumore[12] important clinical signs may only be expected if more than 50 per cent of the pulmonary venous blood drains into the right atrium or its tributaries. This is in accordance with our finding that drainage of all the pulmonary veins of the right lung into the inferior vena cava gives rise to only a comparatively slight disturbance. As Brantigan[13] and Conant and Kurland[14] pointed out, however, partial anomalous pulmonary venous drainage may have a serious effect when a considerable portion of a lung with normal venous drainage is destroyed by a pathologic process or has to be surgically removed. On the other hand we cannot share the opinion of Brantigan that a lung having an anomalous venous drainage constitutes only a burden on the right heart and is useless as regards the ultimate oxygen saturation of the blood. The oxygen uptake from a lung with anomalous venous drainage probably may be regarded as an emergency reserve. Apparently there is a quantitatively rather normal blood flow through the abnormally drained regions, and the oxygen saturation in the pulmonary vein is as high as in any other part of the lung. Bronchospirometric investigations in these cases are lacking so far.

Total Abnormal Pulmonary Venous Drainage

In cases 2, 3, 4 and 5 the diagnosis of total abnormal pulmonary venous drainage through a "left vena cava" into the left innominate vein and superior vena cava seems to be well established clinically and the conventional roentgenogram of the chest seems to be characteristic. Figure 99 (case 33) in Taussig's monograph[15] is virtually identical with the figure-8 shaped roentgenogram in our cases.

It is evident from our series that the condition under discussion is not so rare as was formerly supposed; and moreover a few similar cases have already been reported in the literature, although either they have lacked complete investigation, or have been given a

* This fact could have been further established by injecting Diodrast into a right upper lobe pulmonary artery in the same way as in the third angiocardiographic series of our case 4.

slightly different label. Friedlich, Bing and Blount[9] describe one case (case 25 of their series), without a roentgenologic report, which showed the same pattern; this is apparent from the findings of the heart catheterization studies, and the briefly mentioned postmortem control examination. The latter revealed a common pulmonary venous trunk, which received the blood of all pulmonary veins and which ascended to join the left innominate vein. The authors add that this common trunk was not in close relationship to the tip of the coronary sinus. The foramen ovale was widely patent and led into a small left atrium into which no pulmonary veins entered. The left ventricle was also small. A closely similar case, also verified at autopsy, was reported by the same authors. Here all pulmonary veins joined a common trunk, which drained into the superior vena cava.

Grishman, Brahms, Gordon and King[8] in a publication, which has already been mentioned[8] describe a case studied clinically, which seems to be identical with cases 2, 3, 4 and 5 of our series. The left paramediastinal shadow ("left vena cava") was interpreted as being an unusually wide, aberrant left upper lobe pulmonary vein. The authors believed an aberrant insertion of all pulmonary veins to be a condition incompatible with the continuance of life beyond infancy, whereas their patient of 25 years was asymptomatic with respect to the cardiovascular system.

Another probably identical case was published by Johnson and McRae[17] under the diagnosis of pulmonary venous drainage into the superior vena cava without further specification, as the nature of the right and left paramediastinal mass was not well understood.

Lastly a schematic drawing of the same anatomic condition as found in the case of Taussig and McManus,[15, 16] and in case 25 of Friedlich, Bing and Blount[9] was shown by Gerbode and Hultgren[18] in their article on experimental arteriovenous anastomoses. All clinical details of their case have, however, been reserved for a later publication.*

* Since this paper was submitted for publication, this case has been described by Parsons, Purdy and Bruce (20) showing the same x-ray film as in our cases.

It may be asked why this apparently not so rare condition, which will probably be encountered more often in clinical practice once it becomes more generally known, is not more frequently seen on the autopsy table. The answer might be sought in the relatively slight impairment of health which this anomaly causes so long as the septal defect is sufficiently wide to sustain an adequate systemic circulation. The same contrast between clinical and postmortem experience is present in other conditions, for example, pure pulmonary stenosis which only four years ago was described as a rare anomaly by Taussig,[15] doubtless on the basis of anatomic observations, whereas in our series of cases over the last two years it has been found as an almost common occurrence.

It is of course quite possible that other characteristic roentgenologic configurations in conditions of anomalous pulmonary venous return may also exist. Apart from the two patterns mentioned above we know of only one other, the drainage of all pulmonary veins into the coronary sinus. Inasmuch as the roentgenogram appears to be identical with that reproduced as figure 100 in Taussig's monograph,[15] and since the diagnosis in both Taussig's and our case was established through autopsy* the configuration may probably be said to be characteristic. It differs from the somewhat similar roentgenogram in atrial septal defect mainly in the shape of the enlarged right atrium and the width of the base of the heart.

The symptoms in our cases 2, 3, and 4 of total anomalous drainage were thought to be insufficient to warrant an attempt at surgical relief at the time. In case 5 however an exploratory thoracotomy was carried out, and the diagnosis was at least partly verified at operation. It is conceivable that in some cases, when right heart failure threatens to develop, surgical correction may be urgently required and if this operation should prove to be reasonably

* Our clinical diagnosis, which was not based on any extensive clinical study, had been atrial septal defect with both left to right and right to left shunt. The case will be included in a series of anatomic observations of abnormal pulmonary venous return, to be published later.

safe, operative intervention at an earlier date would be preferred.

It is gratifying therefore to know that Muller[19] was able to perform an anastomosis in two cases between a presumably common left pulmonary vein, which drained into the right side of the heart, and the left auricular appendage with complete success in one case, and a good operative result (although death intervened) in the other case. While these cases probably both presented total anomalous drainage, they do not seem to have been of the same type that is described in this article. From this experience the conclusion may be drawn that surgical correction will be possible in our cases, although the left atrium may be expected to be small, both because the passage of blood through it is less than normal, and because of the fact that part of the atrial wall is missing, which under normal circumstances would have been formed by the incorporation of the common pulmonary trunk into the atrium.

Summary

1. One case of a presumably common right pulmonary vein draining into the inferior vena cava is presented. The diagnosis could be established by means of heart catheterization and angiocardiography; however, like Dotter and co-workers and Grishman and associates we found the conventional chest roentgenogram to be quite characteristic.

2. Four additional cases in which all pulmonary veins appeared to drain into a "left vena cava" connected to the right superior vena cava by way of the left innominate vein are presented. This diagnosis was again based on the results of heart catheterization and angiocardiography (with verification during thoracotomy in one case) but could be made with apparently complete certainty on the grounds of the figure-8 shaped configuration in the conventional chest roentgenogram, as was shown by the constancy of this picture in our own cases and the close similarity to some other cases found in the literature, notably that of Taussig and McManus.

The opinion is expressed that this condition will prove to occur more frequently in clinical practice than has been formerly suspected from anatomic observations.

3. In addition to the aberration of all pulmonary veins, a septal defect must be present, which from both the known anatomic observations and on embryologic grounds (the latter will be discussed in a later paper), can be expected to be a patent foramen ovale or another type of atrial septal defect. In our case 5 the heart catheter was actually passed through this opening; in another (case 4) the overflow from the right atrium to the left appeared to be very likely on the angiocardiogram in the left oblique position. In cases 3 and 4 a venous hum was heard in the region of the superior vena cava (which coincides with the aortic area) while a distinctly different systolic murmur, accompanied by a thrill, was heard at the left lower sternal border. In cases 2, 3 and 4 virtually simultaneous filling of aorta and pulmonary artery was seen after the injection of Diodrast. In view of the presence of a high pulmonary pressure and a very distinct, though narrow, aortic shadow in case 2, the possibility of an Eisenmenger complex was discussed. In all cases an increased pulmonary flow and a slight to moderate oxygen saturation of the arterial blood were present, indicating both left to right and right to left shunts. The diagnosis in case 5 was further substantiated by exploratory thoracotomy.

4. Associated anomalies were found in case 2 (situs inversus abdominis) and case 3 (infundibular stenosis); furthermore a doubtful (relative?) pulmonary stenosis in case 4 was thought to be present.

5. Clinical symptoms were relatively slight but surgical correction may be desirable especially if right heart failure supervenes. The work of Muller is cited in this respect.

6. Apart from the two typical patterns of abnormal pulmonary venous drainage mentioned, only one other type showing a characteristic configuration in the conventional chest roentgenogram is known to us. This is the type in which all pulmonary veins drain into the coronary sinus. The roentgenogram, found by us in one case, which will be discussed in a later article, appears to be identical with that found by Taussig in a case proved by autopsy.

REFERENCES

[1] Brody, H.: Drainage of the pulmonary veins into the right side of the heart. Arch. Path. **33:** 221, 1942.

[2] Smith, J. C.: Anomalous pulmonary veins. Am. Heart J. **41:** 56, 1951.

[3] Edwards, J. E., and du Shane, J. W.: Thoracic venous anomalies. Arch. Path. **49:** 517, 1950.

[4] Edwards, J. E., du Shane, J. W., Alcott, D. L., and Burchell, H. B.: Thoracic venous anomalies. Arch. Path. **51:** 446, 1951.

[5] Zijlstra, W. G.: Fundamentals and applications of clinical oximetry. Groningen. Thesis printed by van Gorcum and Comp. N. V., Assen, Holland, 1951.

[6] Dotter, C. T., Hardisty, N. M., and Steinberg, I: Anomalous right pulmonary vein entering the inferior vena cava: two cases diagnosed during life by angiocardiography and cardiac catheterization. Am. J. M. Sc. **218:** 31, 1949.

[7] Grishman, A., Poppel, M. H., Simpson, R. S., and Sussman, M. L.: The roentgenographic and angiocardiographic aspects of (1) aberrant insertion of pulmonary veins associated with inteartrial septal defect and (2) congenital arteriovenous aneurysm of the lung. Am. J. Roentgenol. **62:** 500, 1949.

[8] Grishman, A., Brahms, S. A., Gordon, A. J., and King, F. H.: Aberrant insertion of pulmonic veins. J. Mt. Sinai Hosp. **17:** 336, 1950.

[9] Friedlich, A., Bing, R. J., and Blount, S. G.: Circulatory dynamics in the anomalies of venous return to the heart including pulmonary arteriovenous fistula. Bull. Johns Hopkins Hosp. **86:** 20, 1950.

[10] Cournand, A., Baldwin, J. S., and Himmelstein, A.: Cardiac Catheterisation in Congenital Heart Disease. New York, Commonwealth Fund, 1949.

[11] Blalock, A.: Surgical procedures employed and anatomical variations encountered in the treatment of congenital pulmonic stenosis. Surg. Gynec. & Obst. **87:** 385, 1948.

[12] Hughes, C., and Rumore, P. C.: Anomalous pulmonary veins. Arch. Path. **37:** 364, 1944.

[13] Brantigan, O. C.: Anomalies of the pulmonary veins. Surg. Gynec. & Obst. **84:** 653, 1947.

[15] Taussig, H. B.: Congenital Malformations of the Heart. New York, Commonwealth Fund, 1947.

[16] McManus, J. F. A.: A case in which both pulmonary veins emptied into a persistent left superior vena cava. Canad. M. A. J. **45:** 261, 1941.

[17] Johnson, A. L., and McRae, D.: Combined use of angiocardiography and cardiac catheterization in the diagnosis of congenital anomalies of the cardiovascular system. Pediatrics **2:** 643, 1948.

[18] Gerbode, F., and Hultgren, H.: Observations on experimental atriovenous anastomoses with particular reference to congenital anomalies of the venous return to the heart and cyanosis. Surgery **28:** 235, 1950.

[19] Muller, W. H.: The surgical treatment of transposition of the pulmonary veins. Ann. Surg. **134:** 683, 1951.

[20] Parsons, H. G., Purdy, A., and Jessup, B.: Anomalies of the pulmonary veins and their surgical significance. Pediatrics **9:** 152, 1952.

The Diagnosis of Congenital Subaortic Stenosis

Application of Hemodynamic Principles

By BERNARD L. BROFMAN, M.D., AND HAROLD FEIL, M.D.

Optically recorded subclavian pulse curves obtained with a simple cup-tambour system give graphic evidence of aortic valve mobility. Differentiation between congenital subaortic stenosis and aortic stenosis was aided by the demonstration in the former of a sharp incisura accompanied by a good aortic second sound; these two features were lacking or rudimentary in the latter. Despite marked auscultatory findings, there is usually little hemodynamic impairment in subaortic stenosis.

SURGICAL treatment of stenotic valvular lesions[1] requires definitive diagnosis. The clinical differentiation of aortic stenosis from congenital subaortic stenosis has always presented certain difficulties. Such factors as age of onset, history of rheumatic fever, and the quality of the second aortic heart sound have aided in the differentiation.[2-5]

Review of the literature indicates that subaortic stenosis is not rare. According to Abbott[6] subaortic stenosis occurred as a primary lesion in 1.2 per cent of 1000 autopsied cases of congenital heart disease (as compared with an incidence of 9.2 per cent for patent ductus arteriosus).

Since Chevers' original description of subaortic stenosis in 1842[7] numerous case reports of the lesion with and without associated anomalies have appeared.[3, 4, 8-17] The relative rarity of the isolated lesion at autopsy as compared with its clinical incidence suggests the benignity of subaortic stenosis. It is also probable that minor degrees are missed at autopsy.

The congenital nature of the lesion described by Keith is generally accepted.[18, 19] Subaortic stenosis is analagous to infundibular stenosis in the right ventricle in that it probably represents an arrest of involution of the bulbus cordis. Usually a fibrous ridge or bar just below the semilunar valves extending 1 mm. to 1 cm. into the ventricular cavity, it consists of much elastic and hyalinized connective tissue covered by intact flattened endothelium. The turbulent passage of blood through the narrowed region may produce some of the fibrous component of the lesion in adults. Figure 1 demonstrates the gross appearance of the lesion in uncomplicated congenital subaortic stenosis, while in figure 2 tetralogy of Fallot associated with subaortic stenosis is shown. Note that the aortic valve itself is not found to be involved.

Grishman, Steinberg, and Sussman[3] collected 23 cases of aortic and subaortic stenosis. They stressed the importance of pulse tracings and phonocardiograms but did not attempt to differentiate aortic from subaortic stenosis. Young[4] presented 10 cases of subaortic stenosis discovered clinically in routine examination of 1800 soldiers. He stated that in this condition the anacrotic pulse of aortic stenosis is not present. Brown[20] has attempted to differentiate between congenital aortic and congenital subaortic stenosis on the basis of clinical signs. Kiloh[21] after study of 15 patients with pure aortic stenosis, all under the age of 50, stated that the lesion is probably not rheumatic and cannot be differentiated from subaortic stenosis (except possibly by angiocardiography).

Levine and Harvey[5] pointed out that in subaortic stenosis there is a loud systolic murmur of greatest intensity in the aortic area associated with a thrill transmitted over a broad area. As contrasted with aortic stenosis, the aortic sound is not decreased and may be

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accentuated because the aortic valve is not involved. Friedberg[2] described the murmur as loud and harsh in the second right intercostal space and radiating to the cervical region. He published an excellent carotid pulse curve and phonocardiogram showing the characteristic features.

FIG. 1. Gross autopsy findings in uncomplicated subaortic stenosis. Note fibrous ridge (arrow). A 66 year old male who died suddenly following onset of severe precordial pain. (Courtesy Dr. C. K. Friedberg and the Department of Pathology of Mount Sinai Hospital, New York.)

GENERAL PRINCIPLES

The pulse curve obtained from the subclavian artery retains all of the characteristics shown in the aortic pulse.[22] In the normal, the steep rise is interrupted by an anacrotic notch or peak due to the sudden increase in velocity of ejection (fig. 3). The curve rises to a rounded peak (maximum ejection). A fall in pressure denotes reduced ejection. A sharp incisura follows (ventricular relaxation), after which one or several small vibrations are observed due to closure of the semilunar valves. During diastole another wave of longer period may be seen.

In aortic stenosis (fig. 4) the subclavian pulse curve begins with a sharp, steep ascent which continues to a level of about one-third to one-half of the height of the upstroke.[25] It ends with a vibration similar in character to that occurring in the normal pulse, differing only in that this primary peak occurs relatively low on the ascending limb instead of at the top. After this primary vibration, the curve rises more slowly, differing from the normal in that the summit is not reached in mid-systole but near the end of systole. The gradual ascent

FIG. 2. Tetralogy of Fallot associated with subaortic stenosis. A 4 year old female with congenital cyanotic heart disease, type undetermined premortem. Typical ridge (arrow) completely encircling subaortic area; lumen was 3 cm. in circumference in this region. (Courtesy Institute of Pathology, Western Reserve University.)

is broken by small vibrations, irregular in amplitude and period, which is the graphic representation of the systolic murmur and thrill of aortic stenosis. On the catacrotic side the fall resembles much the ascent in gradient. The sharp incisura is either lacking or rudimentary, and there are no sharp after-vibrations since the valve rigidity prevents proper closure.

The above description of the pulse in aortic stenosis may be applied to the pulse of sub-

aortic stenosis except that the diastolic fall is more rapid and *there is a sharp incisura, followed by the normal after-vibrations* (fig. 5). Thus, obstruction to ejection produces the anacrotic vibrations, but the normal aortic valve closure produces vibrations caused by the sudden impact of the blood column on the valve.

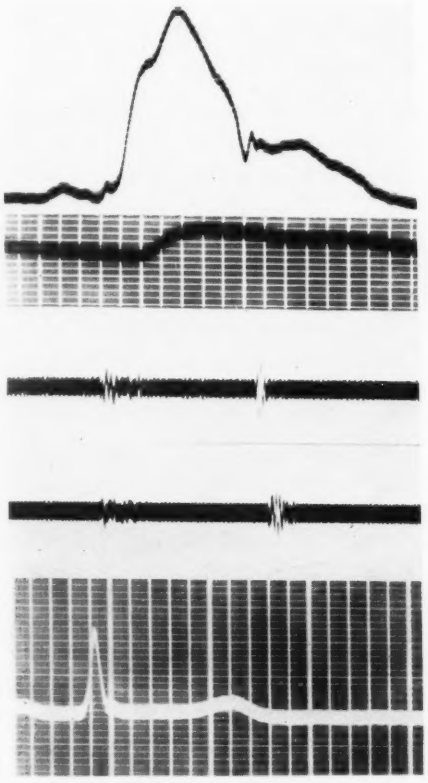


FIG. 3. Normal pulse curves and heart sounds. A 30 year old physician. The tracings shown are: subclavian pulse, radial pulse, heart sounds over aortic area, and over pulmonic area, and electrocardiogram, lead II. The incisura is somewhat lower than usually seen in normals. (Discussion in text.)

In aortic stenosis the leaflets are fused and rigid and no vibrations are seen. The evidence of a faint or absent second heart sound favors the diagnosis of aortic stenosis, but a second sound may be due to a transmitted pulmonary valve closure. The subclavian pulse curve then gives definite and graphic evidence of the presence or absence of aortic valve mobility.

The application of these principles has aided us in distinguishing between aortic stenosis and congenital subaortic stenosis, and has further served as a basis in evaluating certain aspects of the hemodynamics of subaortic stenosis.

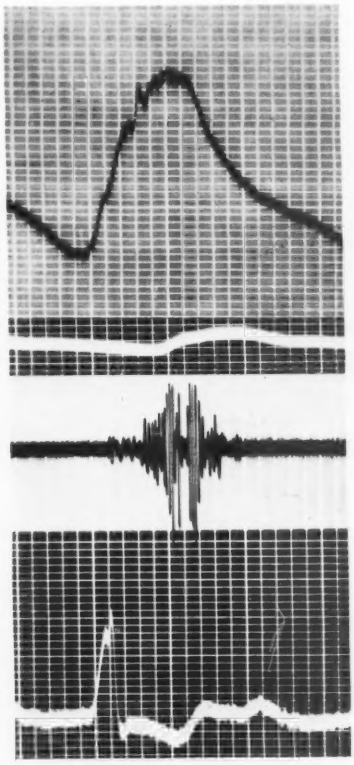


FIG. 4. Aortic stenosis. A 50 year old female with long-standing rheumatic heart disease. Shown are: subclavian pulse, radial pulse, heart sounds over aortic area, and electrocardiogram, lead II. (Discussion in text.)

METHODS AND MATERIALS

In a large series of patients with acquired or congenital heart disease, optically-recorded arterial pulse tracings were obtained in those with suspected aortic valve obstruction. Subclavian and radial artery pulse tracings were obtained by means of a cup-tambour system using a Frank segment capsule and optical registration as described by Wiggers.[24] Heart sound recordings and electrocardiograms obtained with a Sanborn Stethocardiette were superimposed.

Using the method described by Katz and Feil,[25] the duration of isometric contraction and total

systole were determined in selected cases. Pulse transmission time from subclavian to radial artery was measured by noting the difference in time of the upstroke in the two pulse curves.

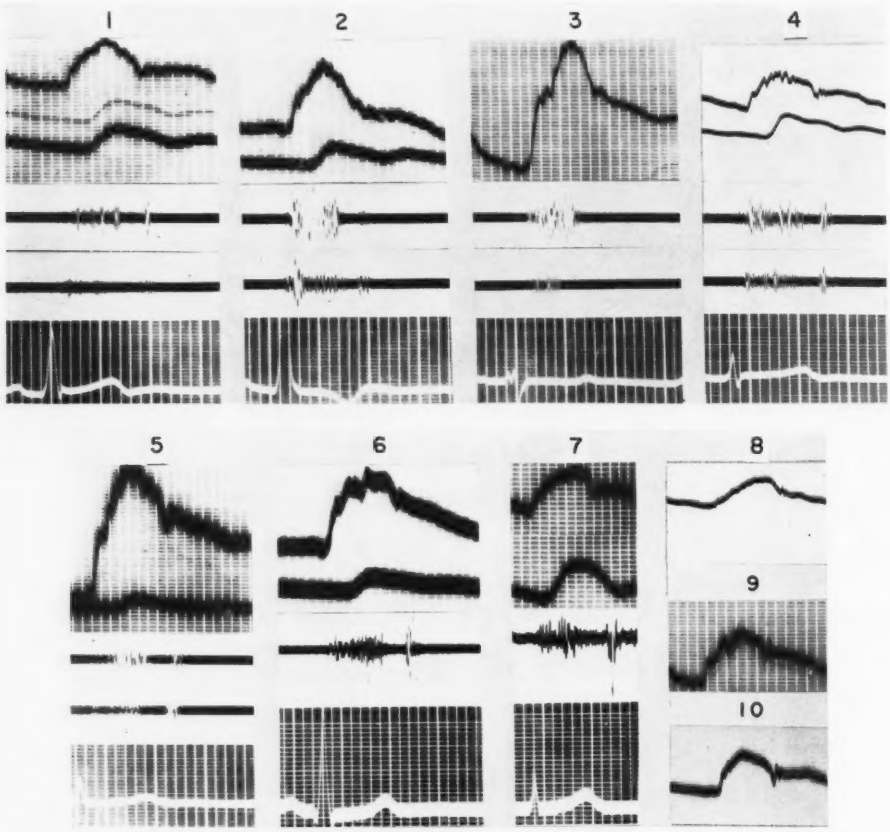


FIG. 5. Subaortic stenosis. Characteristic subclavian and radial artery pulse tracings, and aortic and pulmonic area heart sounds in 10 cases studied. (In cases 8, 9, 10 only the subclavian pulse tracings are illustrated; in case 3, the radial pulse is omitted; in cases 6 and 7, there are only aortic area heart sounds.

RESULTS

In the past two years, 10 patients with suspected congenital subaortic stenosis have been observed. All pulse curves were considered characteristic of this lesion.

Their ages ranged from 3½ to 37 years. All 10 (four females and six males) had the following features in common:

1. Heart murmur present from birth. The murmur, accompanied by a thrill, was characteristically located over aortic area and transmitted toward the great vessels.

2. Normal physical and mental development.

3. No symptoms or disability referable to the lesion.

4. Minimal or no left ventricular enlargement on cardiac fluoroscopy.

5. Blood pressure within normal limits.

The pertinent data in these cases were as follows:

Case 1. A 15 year old boy (high school football player) had a blood pressure of 116/88 and an electrocardiogram showing left ventricular hypertrophy.

Case 2. A 12 year old boy with a blood pressure reading of 110/70 showed left ventricular hypertrophy in the electrocardiogram.

Case 3. A 10 year old boy, had had resection and repair of coarctation of the aorta. Electrocardiogram showed left ventricular hypertrophy before resection of coarctation and left axis deviation after.

Case 4. A 7 year old girl had a blood pressure of 110/70 and left axis deviation in the electrocardiogram.

Case 5. A 27 year old woman had blood pressure of 120/70 and a normal electrocardiogram. Patient had had a full-term pregnancy.

Case 6. A 26 year old man with blood pressure of 130/70 showed early left ventricular hypertrophy in the electrocardiogram.

Case 7. A 37 year old male truck driver had a blood pressure reading of 130/90 and a normal electrocardiogram.

Case 8. A 29 year old woman laboratory technician had a blood pressure of 110/70 and showed early left ventricular hypertrophy in the electrocardiogram.

Case 9. A 9 year old boy had a blood pressure of 80/60 and a normal electrocardiogram.

Case 10. A 15 year old girl with a blood pressure of 105/70 had a normal electrocardiogram.

The pulse tracings and heart sounds are shown in figure 5.

Comparison of the pulse curves with the normal reveals the characteristics to be found in subaortic stenosis. The accompanying systolic murmur and definite aortic second sound associated with the incisura are considered diagnostic. In one patient (case 3) the recorded aortic second sound is of poor quality although the dicrotic notch is present.

Duration of isometric contraction, total systole, and pulse wave transmission time were determined in cases 1, 2, 4, 5, 6 and 7 (table 1).

In the six cases studied, the period of isometric contraction was well within normal limits.[25] Total systole and time of pulse wave transmission from subclavian to radial artery were also within normal limits.

Cardiac catheterization was performed in case 1 to rule out any associated anomaly. Pressures in the pulmonary artery, right ventricle, and right auricle were found to be normal. Cardiac output was 6.5 liters per minute. Brachial artery mean systolic pressure, directly recorded, was 89 mm. Hg. All values were within normal limits.

Hemodynamics

Certain interesting aspects of the hemodynamics of subaortic stenosis and of aortic stenosis may be inferred by liberal and approximate application of the formula derived by Gorlin

TABLE 1.—*Duration of Isometric Contraction, Total Systole, and Pulse-Wave Transmission Time in Six Patients with Suspected Congenital Subaortic Stenosis*

Case	Isometric Contraction (sec.)	Total Systole	Cycle Length	Transmission Time (Subclavian to Radial)
1	0.04	0.32	0.80	0.10
2	0.025	0.285	0.80	0.08
4	0.04	0.30	0.65	0.09
5	0.04	0.31	0.82	0.09
6	0.025	0.305	0.79	0.11
7	0.025	0.28	0.70	0.08

and Gorlin[26] for calculation of the cross-sectional area of the aortic valve:

$$AVA = \frac{AVF}{C \times 44.5 \sqrt{LV_{sm} - BA_{sm}}}$$

AVA = *aortic valve area in sq. cm.*

AVF = *aortic valve flow in cc./second*

$$= \frac{\textit{Cardiac output}}{\textit{systolic ejection period in seconds/minute}}$$

LV_{sm} = left ventricular mean pressure in mm. Hg during systolic ejection

BA_{sm} = brachial systolic mean pressure in mm. Hg

C = empiric constant (although this has not been derived it is assumed to be 1 for purpose of this paper).

The following values obtained during cardiac catheterization of case 1 may be substituted:

Cardiac output = 6.5 liters/minute
Systolic ejection = 25.2 seconds/minute

Therefore

$$AVF = 260 \text{ cc./second}$$

By integration from directly recorded brachial pressure curve:

$$BA_{sm} = 89 \text{ mm. Hg}$$

Substituting these values in the formula we obtain

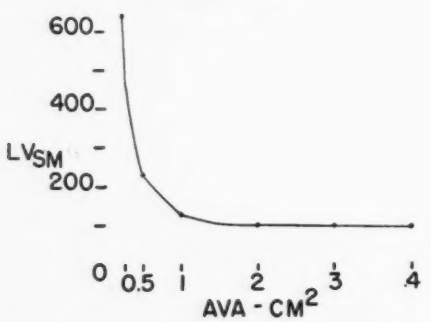
$$AVA = \frac{260}{44.5\sqrt{LV_{sm} - 89}}$$

$$\text{or} \quad LV_{sm} = \frac{34}{AVA^2 + 89}$$

We can now solve for LV_{sm} by substituting assumed values for AVA:

Assumed AVA	LV_{sm}
4 sq. cm.	91 mm./Hg
2 sq. cm.	98 mm./Hg
1 sq. cm.	123 mm./Hg
0.5 sq. cm.	226 mm./Hg
0.25 sq. cm.	639 mm./Hg

These may be plotted:



Thus subaortic (or aortic) narrowing would be expected to produce little significant increase in the left ventricular systolic ejection mean pressure until the valve opening was less than 1 sq. cm.

Discussion

It has been shown previously[27, 28] that the aortic orifice must be reduced to less than one-fourth of its natural size in experimental animals before systolic discharge, the blood pressure, or the pulse pressure are affected. Compensation in aortic stenosis is obtained by increased diastolic volume and intraventricular pressure which causes a more forceful systolic contraction and restoration of normal stroke output in accordance with Starling's Law.[24] In aortic stenosis the isometric contraction period is slightly prolonged, the ejection phase and total systole are considerably prolonged, thus compensating for the reduced rate of ejection.[29]

In this series of cases of subaortic stenosis, isometric contraction is well within normal limits, if not somewhat shortened.[23] Total systole and pulse wave transmission time do not appear to be prolonged.

The superimposition of irregular vibrations on the ascending limb of the central pulse curve corresponds to the systolic murmur and may be present even though the valve area is adequate. It should be emphasized that a loud murmur and definite alteration of the pulse wave contour are not necessarily evidence of dynamic impairment of cardiac ejection. Presumably the outflow tract of the left ventricle would have to be narrowed to less than 1 sq. cm. before any significant load was thrown upon the left ventricle. Rarely is such a degree of subaortic stenosis found.

It has long been obvious that a ventricle with a congenital stenosis of its outflow tract is able to sustain a higher pressure than that in acquired valvular stenosis. In this laboratory we have observed systolic pressures as high as 200 mm. Hg in the right ventricle in patients with isolated congenital pulmonic stenosis with no evidence of failure. The hypertrophy associated with congenital stenosis may be considered developmental as well as compensatory so that the cardiac reserve presumably is relatively normal.

In general it may be said that in isolated congenital subaortic stenosis there may be little or no left ventricular enlargement. The electrocardiogram may be within normal limits or show left ventricular preponderance.[30] Two of our cases (cases 1 and 2) showed a very tall R wave and terminally inverted T wave in the lateral precordial leads.

The presence of a definite incisura followed by after-vibrations gives good evidence of aortic valve closure. When a good second sound is associated with a definite incisura and when the history of a murmur since birth is obtained the diagnosis of subaortic stenosis is readily established.

The need for clear differentiation of congenital subaortic stenosis from aortic stenosis is obvious. The surgical considerations are such that aortic valvular stenosis, congenital or acquired, appears to be amenable to surgery, whereas subaortic stenosis is probably not. The prognosis of uncomplicated subaortic stenosis is much better than that of acquired valvular disease and the lesion may in fact produce little or no disability. Although in some cases of subaortic stenosis the turbulent passage of blood through the narrowed region may produce some of the fibrous component, the stenosis is not progressive as is the acquired valvular lesion. Death from congestive failure in uncomplicated subaortic stenosis occurs late in life.

Reports of subaortic stenosis combined with mitral valve disease have appeared in the French literature.[31, 32] It appears probable that these are cases of acquired endocarditis extending to the subaortic area. Chevers[7] originally stated,

"The part of the orifice immediately below the valves is probably less frequently the seat of marked organic lesions than any other portion of the aortic outlet: still, it is liable to become generally rigid and contracted from inflammatory change; and one portion of its compass—the upper part of the larger part of the mitral curtain which is attached to the bases of the two aortic valves—is occasionally found coated with masses of fibrinous or other deposit: this layer of fibrous structure is also apt to become hardened and rather contracted, after attacks of endocarditis, and in cases of disease affecting the left auriculoventricular orifice; in this way forming a cause of narrowing of the lower part of the aortic ostium, which I believe to be frequently overlooked."

This involvement of the aortic cusp of the mitral valve, producing a type of subaortic stenosis, may account for the anacrotic vibrations of the subclavian pulse and the basal systolic murmur occasionally present in "pure" mitral stenosis.

Summary and Conclusions

The clinical diagnosis of congenital subaortic stenosis can be made with greater certainty with the aid of optically recorded arterial pulse tracings. Subaortic stenosis is distinguished from aortic stenosis by the presence in the former of a sharp incisura accompanied by an aortic second sound of good quality. Pulse tracings obtained in 10 patients fulfilling the clinical criteria for congenital subaortic stenosis demonstrated the characteristic features. The phonocardiograms demonstrated the typical systolic murmur. In one case the aortic second sound was only fairly well heard. The 10 patients, ranging in age from 3½ to 37 years, had no symptoms referable to the congenital lesion.

The clinical frequency of this lesion as compared with the autopsy incidence suggests its benignity in the uncomplicated form. The congenital lesion probably represents an arrest of involution of the bulbus cordis, leaving a fibrous ridge below the semilunar valves. The hemodynamics appear to be such that ordinarily the left ventricle is not greatly burdened by congenital subaortic stenosis. In the absence of subacute bacterial endocarditis or associated anomalies, there is little disability and the prognosis is relatively good. Congestive failure is a late complication.

Subaortic stenosis should be distinguished from aortic stenosis in that the latter may be amenable to surgical treatment.

Acknowledgment

We wish to express our appreciation to Dr. Carl J. Wiggers for his advice and criticism.

REFERENCES

[1] Glover, R. P., Bailey, C. P., and O'Neill, T. J. E.: Surgery of stenotic valvular disease of the heart. J. A. M. A. **144:** 1049, 1950.

[2] Friedberg, C. K.: Diseases of the Heart. Philadelphia, Saunders, 1950.

[3] Grishman, A., Steinberg, M. F., and Sussman, M. L.: Congenital aortic and subaortic stenosis associated with anomalies of the aorta. M. Clin. North America **31:** 543, 1947.

[4] Young, D.: Congenital subaortic stenosis. Am. Heart J. **28:** 440, 1944.

[5] Levine, S. A., and Harvey, W. P.: Clinical Auscultation of the Heart. Philadelphia, Saunders, 1949.

[6] ABBOTT, M. E.: Atlas of Congenital Cardiac Disease. New York, The American Heart Association, 1936.

[7] CHEVERS, N.: Observations on the diseases of the orifice and valves of the aorta. Guy's Hospital Reports. P. 387, 1842.

[8] WALSH, B. J., CONNERTY, H. V., AND WHITE, P. D.: Congenital subaortic stenosis with deformity of the aortic valve; report of case with complicating subacute bacterial endocarditis and mycotic aneurysm resulting in rupture of aorta into pericardium. Am. Heart J. **25:** 837, 1943.

[9] GRUENWALD, P.: Subaortic stenosis of the left ventricle; report of six cases. J. Tech. Methods **27:** 173, 1947.

[10] DITTRICH, F.: Ueber die Herzmuskelentzündung. Vrtljschr. prakt. Heilk. **1:** 58, 1852.

[11] LINDMAN, J. H.: Zur Casuistik seltener Herzenkrankungen. II. Ein Fall von Stenose des Conus arteriosus aortiae. Deutsche Arch. klin. Med. **25:** 510, 1880.

[12] LAUENSTEIN, C.: Ein Fall von Stenose des Conus arteriosus aortiae. Deutsche Arch. klin. Med. **16:** 374, 1875.

[13] MASON, D. G., AND HUNTER, W. C.: Subaortic stenosis. Am. J. Path. **18:** 343, 1942.

[14] THURSFIELD, H. A., AND SCOTT, H. W. Subaortic stenosis. Brit. J. Child. Dis. **10:** 104, 1913.

[15] WIGGLESWORTH, F. W.: A case of subaortic stenosis with acute aortic endocarditis. J. Tech. Methods **17:** 102, 1937.

[16] GREENBERG, J., AND SIMON, M. A.: Subaortic stenosis in an adult. Canad. M. A. J. **61:** 59, 1949.

[17] MORRISON, R. W., AND EDWARDS, J. E.: Subaortic stenosis. Report of two cases, one associated with patent ductus arteriosus, the other complicated by bacterial endocarditis. Bull. Internat. A. M. Mus. **31:** 73, 1950.

[18] KEITH, A.: Schorstein lecture on the fate of the bulbus cordis in the human heart. Lancet **2:** 1267, 1924.

[19] DORMANNS, E.: Zur sogenannten linksseitigen Conusstenose. Beitr. path. Anat. **103:** 235, 1939.

[20] BROWN, J. W.: Congenital Heart Disease. London, John Bale, 1939.

[21] KILOH, G. A.: Pure aortic stenosis. Brit. Heart J. **12:** 33, 1950.

[22] WIGGERS, C. J.: The Pressure Pulses in the Cardiovascular System. New York, Longmans Green, 1928.

[23] FEIL, H. S., AND KATZ, L. N.: The transformation of the central into the peripheral pulse in patients with aortic stenosis. Am. Heart J. **2:** 12, 1926.

[24] WIGGERS, C. J.: The Circulation in Health and Disease, ed. 2. Philadelphia, Lea & Febiger, 1923.

[25] KATZ, L. N., AND FEIL, H. S.: Clinical observations on the dynamics of ventricular systole. 1. Auricular fibrillation. Arch Int. Med. **32:** 672, 1923.

[26] GORLIN, R., AND GORLIN, S. G.: Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. Am. Heart J. **41:** 1, 1951.

[27] ALLAN, G. A.: A scheme of the circulation with experiments to determine the additional load on the apparatus produced by conditions representing valvular lesions. Heart **12:** 181, 1926.

[28] DE HEER, J. L.: Die Dynamik des Sangetierherzens im Kreislauf in der Norm, bei Aortenstenose und nach Strophantin. Pflüger's Arch. ges. Physiol. **148:** 1, 1912.

[29] KATZ, L. N., AND FEIL, H. S.: Clinical observations on the dynamics of ventricular systole. III. Aortic stenosis and insufficiency. Heart **12:** 171, 1925.

[30] PAUL, O., MYERS, G. B., AND CAMPBELL, J. A.: The electrocardiogram in congenital heart disease. Circulation **3:** 573, 1951.

[31] RENDU, H. J. L. M.: Insufficance et retrecissement mitral; retrecissement aortique; hemorrhages pulmonaires multiples; obliteration de l'artere pulmonaire. Bull. Soc. anat. Paris **46:** 235, 1871.

[32] LEMIERRE, A., AND BERNARD, E.: Un Cas De Retrecissement Sous-Aortique. Gaz. d'hôp. **98:** 325, 1925.

Studies of the Mitral Valve. I. Anatomic Features of the Normal Mitral Valve and Associated Structures

By Ian E. Rusted, M.D., Charles H. Scheifley, M.D., and Jesse E. Edwards, M.D.

This study attempts to bring into focus certain details which have not been described adequately in textbooks of anatomy. This information is now of considerable significance because of its role in the genesis and surgical treatment of mitral stenosis. Variations in the size and shape of the mitral valve are described, with particular reference to the fact that valve commissures, or junctional zones between the leaflets, occur in the normal valve. Measurements of commissures, chordae tendineae and valve leaflets are presented, with a discussion of the significance of some of these measurements.

UNTIL recent years, descriptions of the mitral valve in anatomic textbooks were entirely adequate. With the impetus provided by the work of Murray,[1] of Bailey[2] and of Harken and associates,[3] operations for the relief of mitral stenosis are becoming commonplace. Because of this, any anatomic factors which might affect the indications for operation, the technic used, or the postoperative prognosis would seem worthy of more careful consideration. The nature of such anatomic factors and a discussion of their significance form the basis of this communication.

Materials and Methods

Fifty normal hearts were examined. The specimens, which had been fixed in formalin following necropsy, were selected from cases in which there was no evidence of cardiac disease. In some cases there were moderate degrees of coronary atherosclerosis but where there was any evidence of myocardial infarction the specimen was excluded. There were 25 men and 25 women, five men and five women from each decade between the ages of 30 and 79 years.

Measurements were made of the following structures constituting or associated with the mitral valve: (1) the anterior cusp of the mitral valve from its central portion, or apex, along a perpendicular line to its base; (2) the posterior cusp, at a corresponding site; (3) the diameter of the valve from anterolateral to posteromedial commissure, that is, the greatest diameter of the orifice; (4) circumference of the valve ring, with the heart opened; (5) the depth of the junctional tissue, or commissures, between the two cusps, measured from their free edges to the valve ring; (6) the length and thickness of certain chordae tendineae. In measuring thickness of chordae, main stems, that is, origins of these structures, were avoided, their branches being measured.

A pair of dividers with fine points and an ordinary ruler with subdivisions of 0.1 cm. were used, in a conscious effort to use a simple, practical method of making measurements. If a structure, usually a chorda tendinea, was inaccessible it was excised and placed across the ruler in order to obtain a more accurate measurement. In general, therefore, measurements were probably not in error by more than 0.02 or 0.03 cm.

Before considering the results obtained, our discussion of their significance will be made easier by quoting from *Cunningham's Text-book of Anatomy*.[4] Of several standard texts that were examined, this was found to contain the most detailed description of the mitral valve. This description reads, in part, as follows: "The two cusps [of the mitral valve] are triangular and of unequal size. . . . The bases of the cusps are either continuous with each other at their attachments to the fibrous ring around the mitral orifice, or they are separated by small secondary cusps of irregular form and size. . . ." It should be noted that the reference to the continuity of the cusps at their bases suggests that there is little or no valvular tissue separating them, unless a secondary type of cusp exists. In other words, one might be justified in assuming that the point of contiguity could be at the valve ring. Grant[5] referred briefly to "a short cuff" of tissue at this site, but we have no details as to the frequency of its occurrence, its size or its significance.

Figure 1 shows a normal mitral valve which has

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been opened by an incision which passes through the posterior cusp. Where the anterior cusp ends there is a small junctional zone of valvular tissue which merges with the posterior cusp. The term "commissure" has never been applied to this area, although a standard definition of the word "commissure" is given as "a junctional zone." Another definition refers to "areas joined together," and this seems to have been the one intended by Glover,

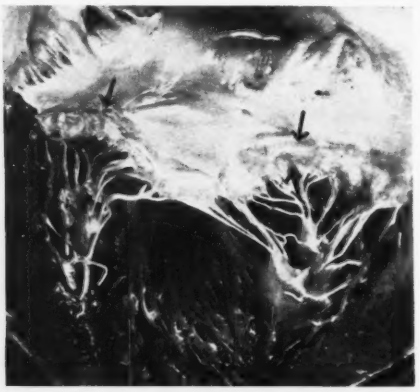

FIG. 1. A normal mitral valve, opened by an incision through the middle of the posterior cusp. Arrows indicate the junctional zones or commissures between the two cusps of the valve.

TABLE 1.—*Measurements (in Cm.) of Normal Mitral Valves (50 Hearts)*

Structures measured	Men (25 subjects)		Women (25 subjects)	
	Average	Range	Average	Range
Anterior cusp	2.3	1.6- 2.9	2.1	1.6- 2.5
Posterior cusp	1.3	0.8- 1.8	1.2	0.7- 2.4
Anterolateral commissure	0.8	0.5- 1.3	0.7	0.4- 1.1
Posteromedial commissure	0.8	0.5- 1.3	0.7	0.3- 1.0
Intercommissural diameter	2.5	1.9- 3.7	2.1	1.5- 3.0
Circumference of valve ring	9.9	8.5-11.0	8.5	7.5-10.5

Bailey and O'Neill[6] when they stated that mitral disease causes the commissures to become an anatomic reality. For reasons which will be made clearer later, we believe that the commissures, the tissue joining the two mitral leaflets, should be considered as anatomic realities in the normal valve. In a modified sense, the area of fusion of leaflet edges caused by rheumatic disease may also be called an artificial or pathologic commissure.

RESULTS

Table 1 contains details of the measurements made in the manner described under Materials and Methods. In none of the hearts examined did the valve orifice extend all the way to the ring; that is, there was always some junctional or commissural tissue between the two cusps of the mitral valve in this series of cases. With very few exceptions the depth of this tissue ranged between 0.5 and 1.0 cm. The figures representing the intercommissural diameter of the valve, with the heart held in the closed position, show a considerable range above and below the equivalent of two fingerbreadths (roughly 2.5 to 3.5 cm.). Thus, a valve less than two fingerbreadths from commissure to commissure is not necessarily stenotic, while one that admits two fingers may be mildly stenosed. In half of the cases the anteroposterior diameter of the orifice averaged 1.5 cm., but the manner in which most of the specimens had been opened made this measurement difficult and the results are therefore not accurate.

It has been our experience that accessory cusps between the two major leaflets are seldom seen (approximately 5 per cent of cases). Frequently the posterior cusp was notched, and it is possible that other observers have considered one of these subdivisions of the posterior cusp as separating the main portions of the anterior and posterior cusps. In doubtful cases we have used the papillary muscles and chordae tendineae to designate the site of the commissure, thus helping to make clear where the posterior cusp begins.*

In table 2 are seen the measurements of chordae tendineae extending from each papillary muscle to the corresponding commissure. In one case there was an anomalous absence of chordae from the anterolateral muscle to the region of the commissure. In another instance this commissure was attached directly to the apex of the papillary muscle, thus accounting for the zero figure in table 2. The other groups of chordae tendineae measured were those which are so important in main-

* See Addendum.

taining the competency of the mitral valve: that is, those chordae going from the papillary muscles to the apex or central portion of the anterior cusp.

It is convenient to remember that the thickness of all individual chordae was less than 0.1 cm. In two thirds of the cases there was a thicker chorda from each muscle (or group of muscles) inserting near the central portion of the anterior cusp, its diameter averaging 0.09 cm. and ranging from 0.06 to 0.16 cm.

In Cunningham's textbook[4] it is pointed out that the ventricular surfaces of the valve leaflets are roughened by the attachments of the chordae tendineae. In Gray's[7] textbook it is stated that "nearly all the chordae tendineae which reach [the anterior cusp] are attached near the margin of this cusp which, therefore, is smooth on both its surfaces. . . ." Figure 2*a* shows the latter arrangement, which is said to provide a smooth surface over which blood may flow into the aorta. We are able to see in this photograph a fibrous band within the endocardial layers of the valve, running along its line of closure. Most of the chordae tendineae appear to insert into this fibrous band. That this is not always the case is shown in figure 2*b*, where the chordal insertions into the anterior cusp can be seen to pass through the substance of the leaflet for a considerable distance. Many variations of both patterns have been observed. In the posterior cusp, the chordae usually traverse most of the distance through the cusp toward its base. In both leaflets the majority of chordae tendineae insert into the free edge and have been called "chordae of the first order" to distinguish them from the chordae of the second order,[8] which end in endocardial folds on the ventricular aspect of the leaflets 0.3 to 0.6 cm. from the free edge. The chordae of the first order are best seen in figure 1 while those of the second order are

TABLE 2.—*Measurements (in Cm.) of Chordae Tendineae in 50 Normal Hearts*

Location	Men (25 subjects)				Women (25 subjects)			
	Length		Thickness		Length		Thickness	
	Average	Range	Average	Range	Average	Range	Average	Range
To anterolateral commissure	1.4	0.3–2.5	0.05	0.02–0.07	1.0	0 –1.7	0.05	0.02–0.07
To posteromedial commissure	1.7	0.8–2.5	0.05	0.02–0.07	1.3	0.9–1.8	0.05	0.02–0.07
From anterolateral muscle to apex of anterior cusp	2.1	1.3–3.0	0.05	0.02–0.09	1.6	1.0–2.3	0.05	0.02–0.08
From posteromedial muscle to apex of anterior cusp	2.2	1.3–3.2	0.04	0.02–0.07	1.8	1.2–2.2	0.04	0.02–0.07

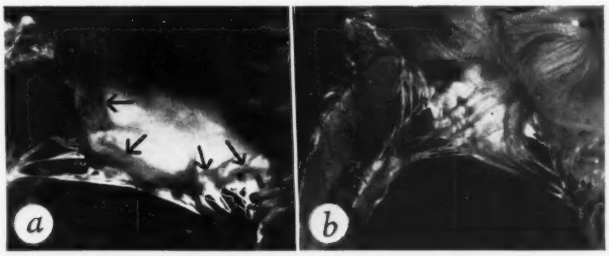

FIG. 2*a*. A normal mitral valve with the anterior cusp transilluminated to show that most of the chordae tendineae insert at or near the free edge of the valve. Arrows point to the fibrous band referred to in the text. (*b*) Transillumination of the anterior cusp of a normal mitral valve to show that many of the chordae tendineae from both papillary muscles pass through most of the valve cusp, in some cases as far as the valve ring.

shown in figure 3. The latter are usually larger in diameter than the former. Between them there may be no other chordae or there may be one or more branches that originate from one or both of the two major groups of chordae. Sometimes these intermediate groups

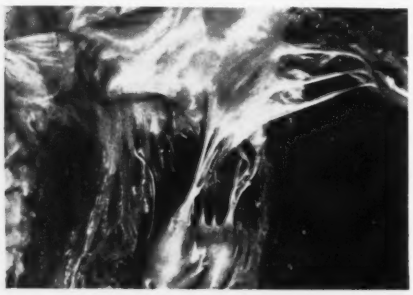

FIG. 3. A normal mitral valve, seen from below, with chordae of the second order inserting into the ventricular surface of the anterior cusp a few millimeters from its free edge.

FIG. 4. Anterolateral portion of a stenosed mitral valve with a single papillary muscle immediately below the pathologic commissure formed by fusion of the edges of the cusps. The chordae tendineae form a network or hammock leading upward from the muscle to the commissure.

of chordae arise independently from the papillary muscles.

Concerning papillary muscles, the textbooks state simply that they are two in number, one superior and one inferior. We have observed that papillary muscles have a consistent relationship to the valve commissures and therefore suggest that they be similarly designated, that is, anterior (or anterolateral) and posterior (or posteromedial). Following a study of 200 normal hearts, we have already reported[9] that the anterior papillary muscle was usually single and that in more than 70 per cent of cases it contained a groove which led in the direction of the commissure immediately above the apex of the muscle. At the posteromedial location there were two or three muscles (or one muscle with two or three heads) in more than 60 per cent of the cases. In almost every instance there was a close relationship between the muscles and the adjacent commissure.

Figure 4 illustrates the way, in this instance in a heart with mitral stenosis, in which chordae tendineae may form a pathway to guide a palpating finger to the commissure. In normal hearts this guiding feature is encountered less frequently at the posteromedial than at the anterolateral site, a fact which may be related to the slightly greater distance between the muscles and the commissure. (See table 2.) Also, multiple muscles at the posteromedial location tend to cause gaps between the groups of chordae arising from them, and these gaps are larger than when a single muscle is present.

Additional Measurements. The thickness of the left atrium, in areas away from the thinner portions surrounding the entry of the pulmonary veins and excluding fatty epicardium, averaged 0.18 cm. (range: 0.1 to 0.3 cm.) as compared with the figure of 0.3 cm. quoted in Gray's[7] textbook. The thickness of the midportion of the left ventricle averaged 1.3 cm. in women (range: 1.0 to 1.6 cm.), and 1.5 cm. in men (range: 1.2 to 1.8 cm.). The 1.8 cm. reading was obtained in a 30 year old man with normal blood pressure. The depth of the left ventricle was measured from the base of the posterior (noncoronary) cusp of the aortic valve to the apex of the left ventricular cavity. In women the measurements averaged 6.7 cm. (range: 5.4 to 8.5 cm.) and in men 7.3 cm. (range: 5.6 to 9.5 cm.).

COMMENT

In discussing the significance of the structures and muscles referred to, possibly the first question that might be asked would be

Why is it important to consider mitral commissures as special parts of the mitral valve? Also, Why is it desirable to differentiate between the commissure which is present normally and the additional artificial commissure that may be produced by fusion of the cusp edges?

Almost all the surgeons doing operations on the mitral valve have stressed the importance of avoiding incisions or tears at any region other than at the commissures. If the method of "finger fracture" is employed, the fact has to be accepted that the weakest point will be the one to separate. If it were possible to predict whether a thickened commissure would separate with ease or only with difficulty a considerable contribution would be made to the equanimity of surgeon and patient. Depending on the severity and the distribution of the rheumatic changes, there may be a small amount of fusion of the cusps (causing a fishmouth type of stenosis) or there may be a great deal of fusion, reducing the orifice to a buttonhole shape. Remembering that the depth of the commissure in the normal valve averaged 0.7 to 0.8 cm. and was never more than 1.3 cm. in our series, the surgeon palpating a stenosed mitral valve may conclude that a commissure deeper than 1 cm. is made up partly of fused cusps. It seems logical that a commissure made up partly of fused cusps might separate more easily than a thickened commissure with no fusion of cusps. In a number of necropsy specimens we have observed that this supposition is usually defensible, and this is one reason for distinguishing between the normally existing commissure and the deeper pathologic commissure.

Whether or not a thickened commissure, with no fusion of cusps, can be broken will depend on the severity and distribution of the rheumatic changes. Very often it is the more severely involved valve with brittle commissural tissue that can be "fractured" rather than the valve with nonbrittle, fibrous commissural tissue.

If the commissure is relatively normal there is obviously no necessity for incising or "fracturing" it. This may seem a superfluous consideration and one would wonder how there can be any stenosis of the mitral valve if the commissures are normal.

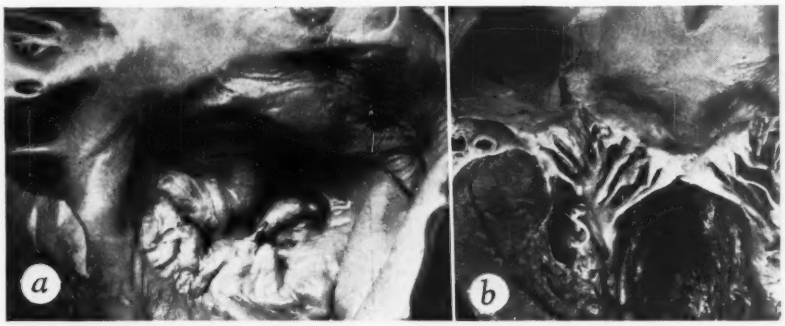

FIG. 5*a*. A stenosed mitral valve, as seen from above. (*b*) The valve shown in *a* after the heart had been opened. Note the thickening of the chordae of the first order. The stiffness of these chordae made it difficult for the valve to open. The anterolateral commissure, at the left, has been incised to help demonstrate its normal appearance.

Figure 5*a* shows the stenosed mitral valve in an adult in whom there had been rheumatic fever in childhood. On physical examination there were presystolic and systolic apical murmurs and the patient also had auricular fibrillation. Cardiac decompensation developed gradually and increased until death occurred from congestive cardiac failure.

Figure 5*b* shows the appearance of the opened valve in this case and demonstrates the fact that considerable stenosis of the mitral valve can exist in the presence of commissures that are normal. The valvular dysfunction seemed to have been caused by chordal

changes. The thickening of the chordae of the first order prevented normal excursion of the valve leaflets and therefore was the basis for mitral stenosis. In this instance the chordae of the second order were only mildly affected, but other cases have been observed in which these chordae were the most severely involved, others in which both sets were equally involved and still others in which all groups of chordae were fused in a solid sheet of stiff fibrous tissue, constituting the main source of valvular dysfunction. Such cases, therefore, belong to the group—fortunately in the minority—in which operations on the commissures would be unsuitable and they present another reason for recognizing the presence of commissures in normal mitral valves and the role which they may or may not play in the genesis of mitral stenosis.

Summary

1. Measurements have been made of the component parts of the normal mitral valve and its associated structures in 50 human hearts.

2. The significance of certain of these structures and their measurements is discussed, with special reference to the normal occurrence and size of the valve commissures.

3. Commissural tissue between the major cusps of the mitral valve averages 0.7 to 0.8 cm. in depth. In mitral stenosis this tissue may remain essentially normal; it may contribute to the stenosis by becoming thick and stiff, or its depth may be artificially increased by fusion of the adjacent margins of the leaflets. It is suggested that this last cause of dysfunction may be suspected if the commissural zones are more than 1.0 cm. in depth.

Addendum

Shortly after the presentation of this material there appeared a communication by Harken and associates.[10] In this they stated on the basis of observations made on 35 normal hearts, that "two additional triangular projections are commonly found that might be called the 'anterior and posterior commissural leaflets.' Four triangular leaflets, arranged circumferentially, constitute the mitral valve." Of the two smaller leaflets they say that "their function in maintaining the integrity of the redundant portions of the two larger valve leaflets in systolic closure would seem to be considerable." The foregoing pattern was seen in 75 per cent of their cases and in the remaining cases any variation was "principally in the size and shape of the ventricular leaflet in relation to the two commissural leaflets."

The foregoing findings led us to examine 50 additional hearts for the presence of accessory cusps. The results, based on the combined total of 100 cases, remain essentially unchanged from our brief statement in the text. In 5 of the 100 normal hearts there were very tiny projections which conceivably could be called "accessory cusps" at one or both commissural sites. In 50 cases the posterior (or "ventricular") cusp was not significantly notched. However, 14 per cent of the cases showed two projections in the portions of the posterior cusp adjacent to the commissures. There was one such projection in an additional 28 cases. In 13 of these 28 cases the notching existed at the anterolateral portion of the posterior cusp and in the other 15 at the posteromedial portion. In three cases the indentation was at the central portion of the cusp so that if the two projections were called "commissural leaflets" there would be nothing to designate as the posterior or "ventricular" cusp in these cases. In each of five cases four so-called cusps constituted the posterior leaflet.

In many of the valves there were no actual indentations but the valve tissue was folded, or actually pleated, so as to create redundant portions. It does seem that such redundant portions and so-called accessory cusps would add to the integrity of the mitral valve during systole. However, these features were absent or inconspicuous in half of our cases even though these hearts apparently functioned as well as the others. For this reason and because of the additional variations encountered we feel it is sufficient to remember that there are two major cusps in the mitral valve, the posterior of which may be regular or irregular along its free margin. It is unusual for an accessory cusp to separate the two major cusps.

REFERENCES

[1] Murray, G.: Surgical treatment of mitral stenosis. Canad. M. A. J. **62:** 444, 1950.

[2] Bailey, C. P.: The surgical treatment of mitral stenosis. (Mitral commissurotomy). Dis. of Chest **15:** 377, 1949.

[3] Harken, D. E., Ellis, L. B., Ware, P. F., and Norman, L. R.: The surgical treatment of mitral stenosis. I. Valvuloplasty. New England J. Med. **239:** 801, 1948.

[4] Brash, J. C.: Cunningham's Text-book of Anatomy, ed. 9. London, Oxford University Press, 1951. P. 1233.

[5] Grant, J. C. B.: A Method of Anatomy; Descriptive and Deductive, ed. 4. Baltimore, Williams & Wilkins, 1948. P. 551.

[6] Glover, R. P., Bailey, C. P., and O'Neill, T. J. E.: Surgery of stenotic valvular disease of the heart. J. A. M. A. **144:** 1049, 1950.

[7] Johnston, T. B., and Whillis, J.: Gray's Anatomy: Descriptive and Applied, ed. 30. London, Longmans, Green & Co., 1949. P. 695.

[8] Tandler, J.: Anatomie des Herzens. In von Bardeleben, Karl: Handbuch der Anatomie des Menschen. Jena, Gustav Fischer, 1913. Vol. 3, pt. 1, p. 88.

[9] Rusted, I. E., Scheifley, C. H., and Edwards, J. E.: Guides to the commissures in operations upon the mitral valve. Proc. Staff Meet., Mayo Clin. **26:** 297, 1951.

[10] Harken, D. E., Ellis, L. B., Dexter, L., Farrand, R. E., and Dickson, J. F., III: The responsibility of the physician in the selection of patients with mitral stenosis for surgical treatment. Circulation **5:** 349, 1952.

The Effects of Vasomotor Drugs and of Anemia upon Interarterial Coronary Anastomoses

By PAUL M. ZOLL, M.D., AND LEONA R. NORMAN, M.D., WITH THE TECHNICAL ASSISTANCE OF SIDNEY CASSIN

The development of functionally significant interarterial coronary anastomoses was measured in 349 young domestic pigs by injecting the coronary arteries with the lead-agar mass of Schlesinger. By this technic well-developed anastomoses were absent in 132 normal control animals. Among the agents tested, acute coronary artery narrowing, sodium nitrite and anemia were effective in stimulating anastomoses. Anastomoses first began to appear two days after narrowing; they became larger and more frequent after seven days.

THE CLINICAL effects of coronary artery occlusion—angina pectoris, myocardial infarction and congestive failure—predominate among the cardiovascular disasters that present themselves repeatedly to the physician. It has become apparent, however, that obstruction of the coronary arteries does not always produce symptoms: in some cases significant clinical and pathologic evidence of myocardial damage may be absent despite longstanding occlusive lesions in the coronary arteries.[1, 2] This apparent inconsistency is explained by the demonstration of larger than normal, functionally significant *interarterial* coronary anastomoses in these human hearts.[3]

Other collateral pathways that have been described consist of intracardiac communications between the coronary arteries, capillaries or veins and the chambers of the heart and also of extracardiac anastomoses between the coronary arteries and pericardial, mediastinal, pleural and pulmonary vessels.[4, 5] None of these extracoronary collateral channels has as yet been clearly demonstrated in human or animal studies to be functionally significant in offsetting the effects of coronary artery occlusion.[6, 7]

Knowledge of the speed of development of interarterial coronary anastomoses and of the conditions that affect it is of great practical importance in the immediate management of coronary artery disease. The obstruction to coronary blood flow by an occlusive process and the compensatory development of interarterial coronary anastomoses are two opposing factors the resultant of which determines the anatomic basis for coronary blood flow. The effects of coronary artery disease on coronary blood flow and, thereby, on changes in the myocardium and their clinical expressions depend in large measure on the relative magnitude and speed of development of these two processes. If interarterial anastomoses could be produced by any means so that the coronary arteries were no longer functionally end-arteries, clinical manifestations of coronary disease would be much less frequent or severe.

In previous studies[8] interarterial coronary anastomoses were produced experimentally in the young domestic pig by acute narrowing of a coronary artery. The coronary collateral circulation that developed after such a sudden narrowing in an otherwise normal heart was effective in protecting the myocardium from the effects of a superimposed complete occlusion. The experimental method also permitted determination of the length of time

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necessary for the development of these intercoronary anastomoses.

The experimental investigations reported below were designed to determine (1) the precise length of time necessary to establish a collateral coronary circulation after acute narrowing of a coronary artery, (2) the effect upon the development of anastomoses of drugs commonly used in the treatment of angina pectoris and myocardial infarction and (3) the effect of pre-existing anemia. The possible beneficial effect of anemia in stimulating coronary collateral circulation was suggested by previous clinical and pathologic studies.[3, 9]

Methods and Technic

The basis for the choice of animal and the methods and technic used in this study are reviewed here briefly. They have been presented in detail in the previous report.[8]

Choice of animal. Domestic pigs were used because their hearts ordinarily do not show interarterial coronary anastomoses when injected with lead-agar mass according to the technic developed by Schlesinger.[10] Fine anastomoses of slight extent were found in only 2 of 134 normal pig hearts injected by this method. Furthermore, in 24 experiments sudden marked narrowing or complete ligation of a major coronary artery always resulted promptly in death of the pig. In dogs, however, intercoronary anastomoses were often found normally and acute coronary arterial ligation did not always produce infarction or kill the animal.[11–13] Following initial narrowing of the right coronary artery to an appropriate degree, extensive functionally significant anastomoses developed in the pig. After a suitable interval of time complete ligation was usually tolerated without death or massive infarction. Upon injection of the coronary arteries the right coronary artery distal to the complete occlusion would be filled by retrograde flow with lead-agar mass from the other coronary arteries. The results with this experimental method in the young domestic pig parallel the events in the human patient with coronary disease: interarterial coronary anastomoses of functional significance are initially absent but may be demonstrated to develop within a suitable time interval after narrowing of a coronary artery.

Operative technic. In the present study, young pigs weighing from 5 to 10 Kg. were used. After premedication with 0.5 mg. atropine sulfate, anesthesia was produced with open-drop ether and maintained with endotracheal ether and oxygen. The heart was exposed by an incision through the third or fourth right intercostal space. The pericardium was opened; the right coronary artery was carefully dissected from its bed 1 to 2 cm. from its origin, and two strands of number 1 Deknatel were passed under it (fig. 1). A steel wire probe 0.8 mm. in diameter was placed alongside the vessel and one of the ligatures was tied snugly around both the wire probe and the artery. The probe was then removed, leaving the vessel narrowed approximately to the diameter of the wire. The duration of the temporary complete occlusion averaged about 20 seconds. The second thread was tucked inside the pericardium and the chest was then closed in layers, with full inflation of the lungs and aspiration of residual pneumothorax. The entire procedure was usually

Fig. 1. Technic of partial narrowing of right coronary artery by ligation of Deknatel over 0.8 mm. wire probe.

completed in 20 to 30 minutes, and the animals were awake and ambulatory within another 20 minutes. After a time interval of two, four, or seven days, the incision was reopened and the second ligature was located. It was then tied tightly so as to occlude completely the right coronary artery at the site of the previous narrowing. Animals that survived the complete occlusion were sacrificed four hours later. In some animals only one of these two operative steps was performed.

Administration of drugs and production of anemia. Some pharmacologic agents that are thought to have a vasodilator or vasoconstrictor action on the coro-

nary circulation were given intramuscularly to animals two or three times daily to study any possible effect in stimulating anastomoses. In no instance did the drug itself appear to have an adverse effect upon the animal. The doses of the medications were similar to those administered to animals by other investigators or larger than those used in clinical practice. They were aminophylline (theophylline ethylenediamine), 15 mg. per kilogram; papaverine, 5 mg. per kilogram; quinidine sulfate, 20 mg. per kilogram; khellin,* 50 mg. per dose; sodium nitrite, 100 mg. per dose; vasopressin (Pitressin), 2.5 pressor units per dose; adrenocorticotropic hormone (ACTH) 5 mg. per dose.

In addition, anemia was produced in a group of 21 animals by repeated small bleedings from the jugular vein with the animal under light ether anesthesia.[14] Depending on previous hematocrit levels and the condition of the animal, the amounts of blood withdrawn varied from 50 to 150 ml. and the intervals between venesections ranged from one to six days. The level of anemia was measured by hematocrit determinations. Hematocrit levels, which averaged 41 per cent in normal pigs, were reduced after bleeding to 13 to 29 per cent, with an average of 21 per cent. These anemic levels were maintained with little variation in all animals for 7 to 14 days. The anemic animals were weak and puny and did not gain weight normally.

In one group of experiments the drugs or anemia were applied for long periods without prior coronary artery narrowing. An agent effective in this way may be regarded as having a *prophylactic* action in protecting the myocardium against the results of subsequent coronary artery occlusion. Sodium nitrite was given to four animals for two weeks, papaverine to eight animals for four to six weeks, and aminophylline to seven animals for three to six weeks; similarly anemia was maintained in 14 animals for one to two weeks. Finally, the right coronary artery was completely occluded without preliminary narrowing in some of these animals to test possible survival. The remaining animals were sacrificed without any coronary artery surgery.

In other experiments the drugs were given only during the interval between initial coronary artery narrowing and death of the animal from final complete occlusion or sacrifice. This procedure tests the *therapeutic* effect of the agent in speeding the rate of development of anastomoses after the onset of coronary artery narrowing and parallels the manner in which these drugs usually are given clinically.

Pathologic methods. The coronary arteries were examined post mortem according to the injection plus dissection technic of Schlesinger.[10] The left descending, left circumflex and right coronary arteries were cannulated and injected separately with differently colored, lead phosphate–agar mass. When the right coronary artery had not been ligated antemortem, it was occluded during the injection so as to make all the injections comparable and to make more evident even a slight retrograde anastomotic filling of the distal vessel with mass of any color. The heart was then unrolled so that all the coronary arteries lay in one plane, a roentgenogram was taken and the arteries were dissected with the aid of the film.

The lumen of the right coronary artery was measured by calibrated probes at the narrowed area and also at adjacent normal segments. The original diameter of the right coronary artery measured between 1.8 and 2.2 mm.; the vessel was always completely occluded by the second ligature. The degree of narrowing produced was fairly uniform, being generally from 15 to 35 per cent of the original cross sectional area, the range previously found[8] to be effective in stimulating anastomoses. The myocardium was examined for gross infarction and necrosis and representative sections were taken for microscopic study.

Criterion of anastomosis. A variety of criteria have been used as measures of the presence of functionally significant intercoronary anastomoses. They include transfer of injected materials of many varieties between coronary arteries, increased survival of animals and reduction in electrocardiographic abnormalities or area of infarcted muscle following coronary artery occlusion. The anatomic demonstration of anastomoses by a lead-agar injection mass which is confined to the arterial tree was the criterion selected in this study. In previous studies anastomoses demonstrated by this technic have been found to be functionally significant in obviating the effects of coronary artery occlusion; furthermore, they are generally absent in normal human or pig hearts.[3, 8]

According to criteria previously described[3] anastomoses were determined upon careful examination of the injected vessels with the aid of the roentgenogram in three ways: (1) by finding a mixture of colors of the injected lead-agar mass; (2) by the presence of mass of any color distal to the occluded right coronary artery or (3) by demonstrating a continuous, macroscopic arterial pathway between two coronary arterial branches. Anastomoses were readily graded quantitatively in distinct groups. Slight (1+) anastomosis consisted of a few particles of mass in the peripheral portion of the right coronary artery or of a barely visible, usually incompletely injected connecting loop between two branches. Moderate (2+) or marked (3+) anastomosis consisted of extensive filling, incomplete (2+) or complete (3+), of the peripheral portion of

* The khellin used in this study was "Eskel," trademark for a product supplied for the investigation by Smith, Kline and French Laboratories through the courtesy of Mr. C. W. French.

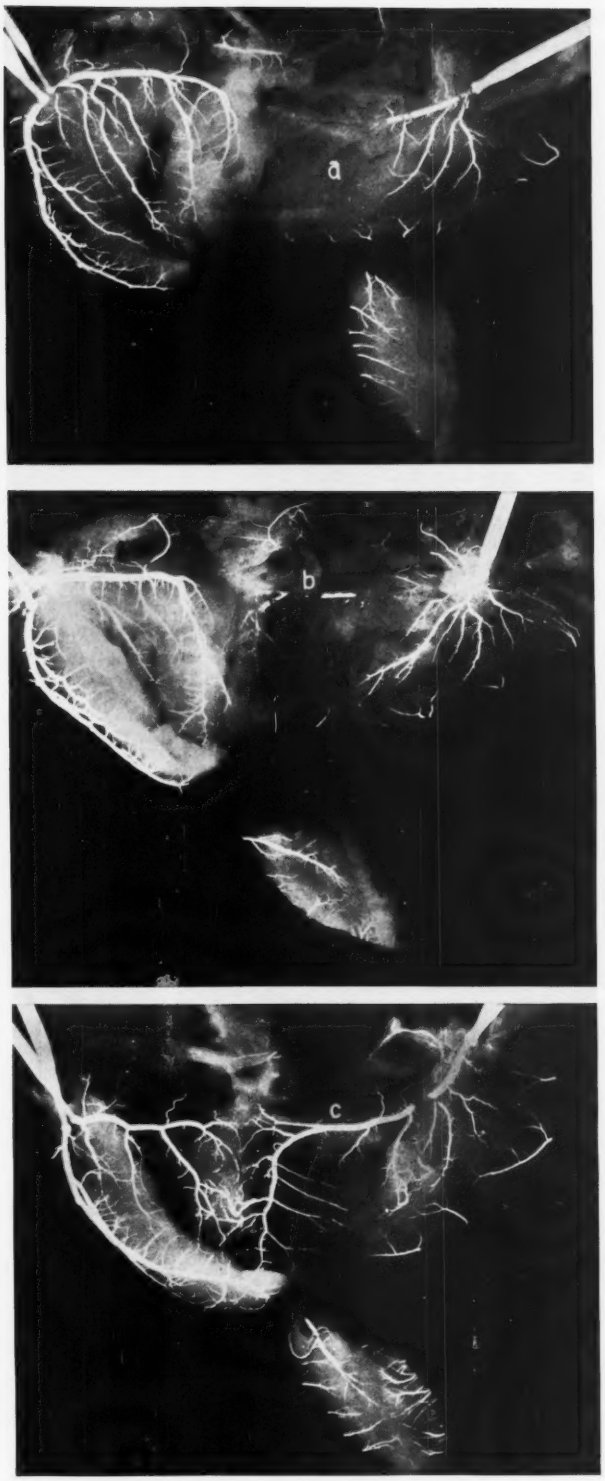

FIG. 2. Roentgenograms of injected pig hearts showing varying grades of anastomoses distal to occlusion of right coronary artery: (*a*) slight (1+); (*b*) moderate (2+); (*c*) marked (3+) anastomoses.

the right coronary artery, usually with a mixture of colors. In figure 2 examples of these three degrees of anastomosis are shown. The two greater degrees of anastomosis represent large, well-developed anastomoses that were never found in normal untreated pigs. Slight (1+) anastomoses were found only rarely in normal pigs (2 of 134 hearts). Extensive anastomotic fill of moderate (2+) or marked (3+) degree was used in this study as the most satisfactory criterion of interarterial coronary anastomoses. Use of this criterion permits determination of anastomoses in large groups of animals that need not be subjected to surgical ligation of the coronary arteries.

Although survival of the animal after complete ligation of a coronary artery depends primarily on functional interarterial anastomoses, many other unrelated factors influence it significantly. The physical vigor of the animal, the depth, duration and smoothness of anesthesia and endotracheal insufflation, the duration and difficulty of the procedure, the amount of manipulation of the heart and its fibrillation threshold, the precise level of the ligature,[15] and the occurrence of various surgical accidents and complications, such as hemorrhage and atelectasis, may all affect survival and their relative importance is often difficult to assess accurately.[16] In our series survival after complete occlusion did correlate roughly with the demonstration of anastomoses by the injection technic, but it was considered a much less satisfactory criterion.

The effect of drugs on coronary collateral circulation has been measured by the extent of acute myocardial infarction as observed grossly on the surfaces of the heart.[17–19] Accurate measurement of infarcts is difficult, however, because of their irregular, wide borders and variable extent on the two surfaces and intramurally.[20] The wide variation of size of infarcts under apparently uniform conditions also makes size of infarction a relatively unsatisfactory criterion.[21]

Electrocardiographic tracings of standard, bipolar limb leads I, II, and III were taken at frequent intervals during both operative procedures and particularly at the times that the coronary artery was dissected, narrowed and occluded. The observed changes in rhythm, in T waves, S-T segments and QRS complexes were those generally recognized as representing varying degrees of myocardial irritability, ischemia, injury and necrosis. The electrocardiographic abnormalities were useful in indicating the degree of coronary artery narrowing and in foretelling the likelihood of death or survival of the animal. But they were not satisfactory measures of anastomoses and could not be used as criteria of the effect of drugs upon coronary blood flow.

Statistical method. Because of the many variables involved in this study, the number of animals in any one category was necessarily small. Furthermore, anastomoses were infrequent or absent in many of the control groups. The "exact test" of Fisher*[22] was therefore applied to determine whether the observed frequencies of anastomoses in test groups and control groups differed significantly. It should be emphasized that this statistical method depends on the "null hypothesis," and answers the specific question: "On the hypothesis that there is no difference between two groups, could a difference as large as the one observed be the result of random variation?" A probability less than 5 per cent ($p < .05$) may be considered as a negative answer to this question and proves the presence of a statistically significant difference. An affirmative answer ($p > .05$) is not evidence of a lack of difference between the two groups, but merely indicates that there is no evidence about it in the data. The statistical method can demonstrate a significant difference, but it cannot demonstrate the absence of a difference between two groups.[23]

Results

Table 1 presents the results obtained in this study of 349 animals. Although the experiments fall into a large number of groups, they may conveniently be regarded as consisting of three general classes. In an untreated group ("control" column) the natural incidence of anastomoses in unoperated animals and the speed of their development after initial narrowing were observed. A second group ("prophylactic group") was treated *prophylactically* by drugs or anemia; the production of anastomoses by these measures was noted without prior coronary artery narrowing. A third group (remainder of table 1) was treated with drugs or anemia during the interval between initial coronary artery narrowing and death; in these animals the combined effects of narrowing plus medication on anastomoses were observed.

Control Animals

The control experiments consisted of two groups of animals that were not treated with drugs or anemia.

(1) One group was composed of 134 normal pigs that were not subjected to surgery and were not treated with any drug or other agent.

*

a	b	a + b
c	d	c + d
a + c	b + d	n

$$p = \frac{(a+b)!\,(c+d)!\,(a+c)!\,(b+d)!}{n!\quad a!\quad b!\quad c!\quad d!}$$

Extensive (2+ or 3+) anastomoses were not found in any of these animals and only two of them showed slight (1+) anastomoses, so that the natural or spontaneous incidence of anastomosis of any degree was established at 1 per cent.

gical accidents or from excessive coronary artery narrowing. Slight (1+) anastomoses were found in one of these 11 animals, an incidence which does not differ significantly from the control group ($p = .23$). The development of anastomoses is first apparent two days after

TABLE 1—*Results in 349 Pigs of Narrowing, Drugs and Anemia upon Interarterial Coronary Anastomosis*

	Degree of Anastomosis	Controls (No Drug)	Sodium Nitrite	Papaverine	Aminophylline	Quinidine	Khellin	Vasopressin	ACTH	Anemia
Prophylactic Group—No Preliminary Narrowing										
	0	132	3	8	7			3		12
	1+	2	0	0	0			0		0
	2+	0	1*	0	0			0		2*
	3+	0	0	0	0			0		0
Preliminary Narrowing 0–7 Days Before Death										
0–1 day	0	10	3		4	1	2		2	
	1+	1	0		0	0	0		1	
	2+	0	1		0	0	0		0	
	3+	0	0		0	0	0		0	
ℵ survivors		0	0		0	0	0		0	
2 days	0	8	14	8	4	5	4		1	5
	1+	2	4	2	2	3	4		3	0
	2+	2	3	2	3	1	0		1	1
	3+	0	4*	0	0	0	0		0	1
$\aleph_5^7$ survivors		6	9	7	3	3	3		2	2
4 days	0	4	9		2	8	7	7		
	1+	1	0		0	2	0	0		
	2+	1	0		0	1	1	1		
	3+	1	1		0	3	1	1		
ℵ survivors		6	5		0	10	1	3		
7 days	0	5			4		2			
	1+	1			0		1			
	2+	3			0		0			
	3+	1			0		0			
ℵ survivors		3			1		0			

ℵ = Number of survivors after complete occlusion.
* = Significantly different from control group.

(2) The second group was composed of 40 control animals in whom varying intervals up to seven days elapsed between initial narrowing of the right coronary artery and death. Eleven of them died within the first day after the initial operation from anesthetic or surinitial narrowing in the finding of 2 of 12 hearts with extensive anastomoses ($p = .0006$). The natural rate of development of anastomoses in untreated animals is reflected in the increasing incidence of 2+ and 3+ anastomoses from two to seven days after narrowing. Ex-

tensive anastomoses, however, are not very frequent until after 12 days; they were found in 7 of 12 animals that survived 12 to 21 days after initial narrowing.[8] Application of these results in young pigs to clinical situations in adult human patients is precarious. They suggest, however, that in pigs anastomoses begin to develop early but full protection from them cannot be generally expected before 12 days or more after coronary artery narrowing or occlusion.

Animals Treated Prophylactically before Coronary Artery Narrowing or Occlusion

In this group of experiments the effect of potent vasomotor drugs and of anemia upon intercoronary anastomoses was tested prior to the production of a local need for anastomosis by coronary artery ligation. An agent that could stimulate the development of interarterial coronary anastomoses even before the appearance of coronary atherosclerosis would obviously be of great clinical value in the prophylactic treatment of coronary disease. Repeated dilatation of the coronary capillary bed by a potent vasodilator might, for example, lead to the enlargement of the normally present, but functionally inadequate, fine intercoronary anastomoses.

Sodium nitrite, papaverine and aminophylline were given to 18 animals over intervals of two to six weeks before acute complete coronary artery occlusion (table 1). Anastomoses were found in one of the four animals treated with sodium nitrite but in none of the others. This single instance of 2+ anastomoses in one of four pigs treated with sodium nitrite is significantly different from their complete absence in the control group of 134 pigs ($p = .03$).

A comparable effect of papaverine or aminophylline on anastomoses was not observed. No anastomoses were found in eight animals treated with papaverine and in seven treated with aminophylline. To demonstrate a significant *positive* effect ($p < .05$) upon anastomoses of any agent in comparison with the control group of 134 hearts, at least one instance in seven hearts of 2+ or 3+ anastomoses would be necessary. To demonstrate the *absence* of an effect of these agents on anastomoses, they must be contrasted with some factor, such as coronary artery narrowing, which does stimulate anastomoses. Calculations show that it would require at least 40 experiments without any 2+ or 3+ anastomoses to demonstrate that these agents differ significantly ($p < .05$) from the slight positive effect of preliminary narrowing of two days' duration.

When the data already obtained are contrasted with the marked effects of *prolonged* narrowing of 12 to 21 days, statistical analysis shows that papaverine and aminophylline are significantly less effective in stimulating anastomoses ($p = .01$ and $.02$).

In a similar manner vasopressin was administered for four days to three animals. Its powerful coronary vasoconstrictive effect might be expected to produce myocardial ischemia comparable to preliminary coronary artery narrowing and might, thereby, stimulate anastomoses. All three animals, however, died promptly after acute occlusion of the right coronary artery and none showed interarterial coronary anastomoses. The number of experiments was too small, however, to demonstrate the presence or absence of an effect of vasopressin upon intercoronary anastomoses. Here also, at least one positive result in seven experiments or a total of 40 negative experiments would be required to prove the presence or the absence, respectively, of a significant effect of vasopressin upon anastomoses.

The effect of anemia, uncomplicated by coronary artery narrowing, was tested in 14 animals. Four pigs died of excessive blood loss or anesthesia before undergoing surgery. Of the remainder, eight died immediately following acute occlusion of the right coronary artery, but two survived acute occlusion and were sacrificed four hours later. Upon injection of the coronary arteries two hearts with well-developed (2+) anastomoses were found among the 14 anemic pigs. This observation is of high statistical significance whether compared with the absence of 2+ anastomoses in the 134 control hearts ($p = .008$) or, disregarding degree of anastomosis, with two instances of 1+ anastomoses in the 134 controls ($p = .04$). No further correlation was found in these

experiments between interarterial coronary anastomoses and variations in the degree or duration of anemia.

Therapeutic Effect of Agents Following Initial Coronary Artery Narrowing

In this series of experiments the effect of vasomotor drugs, of adrenocorticotropic hormone and of anemia upon the rate of development of interarterial coronary anastomoses was tested at varying intervals of time following initial, adequate coronary artery narrowing. The drugs were administered immediately prior to and following the initial procedure of coronary artery narrowing and three times daily thereafter until the animal died or was sacrificed. Anemia was produced by repeated venesections for one to several weeks before the initial operation. The effectiveness of these agents was assessed by comparing animals treated with the various agents with untreated, control animals kept the same time interval between initial narrowing and final complete occlusion with respect to the incidence of extensive anastomoses. Particular emphasis was placed on the two-day interval between narrowing and occlusion because this was the shortest interval in which extensive (2+ or 3+) anastomoses were found in control experiments.

In 14 animals treated with sodium nitrite, aminophylline, quinidine, khellin or adrenocorticotropic hormone death occurred within a few minutes to 24 hours after initial narrowing. The number of injections of drugs ranged from one dose given before the operative procedure to three doses given in the first 24 hours. In only one instance were extensive (2+) anastomoses found: this animal was given one injection of sodium nitrite before operation and it died 13 minutes after narrowing of the right coronary artery to 25 per cent of its original area. These results with sodium nitrite are not significantly different, however, from the findings in the remaining treated or untreated animals that died within the first day after initial narrowing ($p = .16$).

Among the remaining experiments with time intervals from two to seven days between initial narrowing and final occlusion, sufficient time elapsed to permit a number of doses of drugs to be given. A significant difference between the untreated and control experiments in all these groups was found only in the animals treated with sodium nitrite during a two-day interval between narrowing and occlusion. The significant comparison was in the incidence of 3+ anastomoses in this group and all the other control or drug-treated animals in the two-day series ($p = .008$). No other drug showed a favorable or retarding effect upon the rate of development of anastomoses in this or any other time interval. Although anemia was found in the prophylactic study to stimulate anastomoses, a significant additive effect of the two factors of anemia and narrowing was not observed. In the presence of the positive effect of narrowing, a very large number of experiments is required to demonstrate an additional positive factor of slight or moderate effectiveness.

Immediate Effect of Vasomotor Drugs on Coronary Arterial Spasm

During the operative procedure it was observed that some of the drugs had an immediate effect upon coronary arterial spasm. When the right coronary artery was isolated and the threads passed under it, marked spasm of the arterial wall was usually noted in the untreated animal. In animals treated with khellin, aminophylline and sodium nitrite, vasospasm of this type in response to local manipulation was usually much less marked or entirely absent. This type of observation was not quantitated, but it appeared to be generally true and was observed repeatedly. The relation of these observations to the development of interarterial anastomoses was not investigated in this study. Such effects upon vasomotor control of the coronary arteries may well be of some clinical importance.

Electrocardiograms taken at frequent intervals during the procedures offered evidence substantiating the demonstration of anastomoses by the injection technic. In animals in whom no anastomoses were subsequently found, marked S-T and T-wave changes usually appeared following complete ligation. Slight changes occurred after complete ligation in

animals with extensive anastomoses. When anastomoses developed which protected the heart against the effects of complete final ligation, relatively little myocardial damage and little electrocardiographic changes were produced. As previously indicated, however, neither anatomic myocardial damage nor electrocardiographic change was a suitable index of the adequacy or rate of development of interarterial coronary anastomoses.

Discussion

In these experiments the length of time necessary for the development of interarterial coronary anastomoses was determined in the young pig and the effects upon it of various commonly used drugs and of anemia were assessed. Functionally significant anastomoses began to appear very shortly after initial narrowing in otherwise untreated, control animals: they were found occasionally within two days after narrowing and with increasing frequency in seven days. These new, functionally significant collateral pathways may form by the dilatation of previously existing, finer capillary communications or by the growth of entirely new vessels. The rapidity of their appearance, within two days after narrowing, does not contravert either mechanism. Rabinovici and Fine[24] found macroscopic evidence of new blood vessels crossing from adherent omentum to bowel wall within three days after occlusion of a mesenteric artery or vein. Within six hours they saw a new capillary crossing a large thrombus and a perithelial reaction about capillaries suggesting a process of conversion to arterioles.

Of all the drugs studied sodium nitrite alone was found to speed the rate of development of anastomoses. It was effective when given prophylactically to normal pigs and also when given after coronary artery narrowing. These results indicate that vasodilator drugs of this type may have clinical value in addition to their transient vasomotor action: they may change the fundamental anatomy of the coronary system by stimulating interarterial anastomoses so that the coronary arteries are no longer functionally end-arteries.

Anemia was also an effective stimulus for the occasional production of interarterial coronary anastomoses in the absence of coronary arterial narrowing. This finding confirms experimentally in the domestic pig previous clinico-pathologic observations in humans that anemia stimulates interarterial coronary anastomoses[3] and increases coronary perfusion rates.[9] From these observations it appears that anemia may occasionally have a beneficial effect in coronary artery disease. Anastomoses stimulated by pre-existing anemia (either spontaneous or purposefully induced anemia) may protect the myocardium from the effects of coronary artery occlusion and diminish or obviate entirely clinical symptoms of coronary disease. It is well recognized, however, that anemia of marked degree or rapid development may aggravate clinical symptoms of coronary artery disease and even precipitate myocardial infarction.[25,26] Deleterious effects of anemia on the myocardium have been reported by us and by others as well.[3, 27] Our previous observations indicate that the potentiality of anemia to stimulate intercoronary anastomoses is intimately related to its capacity to produce myocardial damage. Anemia may stimulate anastomoses by producing tissue anoxia and vasodilatation; if the anemia is of marked degree, however, irreversible tissue damage may occur. Although these two abnormalities are produced by varying degrees of cardiac anoxia from any cause, nevertheless they do not always appear together. In some instances anastomoses produced by anemia are sufficiently protective to forestall or diminish the development of myocardial damage even in the presence of severe coronary artery disease. A critical degree of anemia may be found which will stimulate anastomoses and yet will not result in significant myocardial lesions. Anemia may then conceivably have some therapeutic application in the treatment of patients with coronary artery disease.

Unfortunately, none of the agents studied exhibited a striking or constant effect in stimulating interarterial coronary anastomoses. Extensive anastomoses were not produced uniformly or even in the majority of animals in

any of the experiments. Anemia, drugs and even previous coronary artery narrowing cannot be relied upon with assurance to prevent the dire effects of coronary artery occlusion or to hasten the time of re-establishment of adequate coronary blood flow. The inconstancy of success in producing anastomoses suggests that unrecognized factors may be of critical importance in this process. The degree and duration of narrowing have been established as important factors. Whether the degree and duration of anemia are of major or great importance appears questionable from the preliminary observations made in this study and in the clinicopathologic study of human material.[3]

It must be emphasized that only one very special attribute was tested of the various agents examined, namely, their effect upon the speed of development of interarterial coronary anastomoses as measured by the special methods of this study. Many other characteristics more or less unrelated to this attribute might be more important in determining their applicability to clinical situations. Such factors include effect on blood flow in the coronary bed distal to a narrowing or occlusion, relative effect on coronary and systemic vasodilatation and effect on cardiac output. For example, their lack of effect on anastomoses notwithstanding, several of the drugs did reduce local coronary arterial spasm following local irritation. These drugs may thus be of clinical value to patients with coronary artery disease by mechanisms unrelated to their effect on intercoronary anastomoses.

These experiments reaffirm the efficacy of coronary artery narrowing, or of relative cardiac anoxia produced by any means, in stimulating anastomoses. They do not, however, bear on the basic mechanisms by which this is accomplished. The length of time necessary to establish collateral coronary circulation after acute coronary arterial narrowing in young pigs has been established more precisely. This technic may therefore be used as a tool to investigate many of the problems concerning interarterial coronary anastomoses that are still unsolved.

Summary

The length of time necessary for the development of interarterial coronary anasto moses and the effects upon it of some vasomotor drugs and anemia were determined in 349 pigs by an injection plus dissection study of the coronary arteries.

Functionally significant anastomoses first appeared two days after narrowing of a coronary artery and became more frequent after seven days.

Sodium nitrite showed significant effect in stimulating anastomoses when given prophylactically to normal pigs and when given therapeutically after coronary artery narrowing. Anemia also stimulated anastomoses significantly in normal pigs and occasionally protected animals against subsequent acute coronary artery occlusion.

REFERENCES

[1] Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: Angina pectoris, coronary failure and acute myocardial infarction. The role of coronary occlusions and collateral circulation. J.A.M.A. **116:** 91, 1941.

[2] —: The pathogenesis of angina pectoris and some clinical implications. Cincinnati J. Med. **31:** 205, 1950.

[3] Zoll, P. M., Wessler, S., and Schlesinger, M. J.: Interarterial coronary anastomoses in the human heart, with particular reference to anemia and relative cardiac anoxia. Circulation **4:** 797, 1951.

[4] Batson, O. V., and Bellet, S.: The reversal of flow in the cardiac veins. Am. Heart J. **6:** 206, 1930.

[5] Wearn, J. T.: The anatomy of the coronary vessels. In: Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain. New York, Macmillan, 1936. Pp. 31–56.

[6] Zoll, P. M., Wessler, S., Schlesinger, M. J. Freedberg, A. S., and Blumgart, H. L.: Interarterial coronary anastomoses. Modern Concepts Card. Dis. **21:** no. 1, Jan. 1952.

[7] Gregg, D. E.: Coronary Circulation in Health and Disease. Philadelphia, Lea & Febiger, 1950. P. 200.

[8] Blumgart, H. L., Zoll, P. M., Freedberg, A. S., and Gilligan, D. R.: The experimental production of intercoronary arterial anastomoses and their functional significance. Circulation **1:** 10, 1950.

[9] Zoll, P. M., and Dresdale, D. T.: The flow through the coronary bed in normal and abnormal human hearts by the method of kerosene perfusion (Abstract). J. Clin. Investigation **27:** 564, 1948.

[10] Schlesinger, M. J.: An injection plus dissection study of coronary artery occlusions and anastomoses. Am. Heart J. **15:** 528, 1938.

[11] Piannetto, M. B.: The coronary arteries of the dog. Am. Heart J. **18:** 403, 1939.

[12] Mendlowitz, M., Shauer, G., and Gross, L.: Hemodynamic studies in experimental coronary occlusion. II. Closed chest experiments. Am. Heart J. **13:** 663, 1937.

[13] Bobb, J. R. R., Kunze, D. C., McCall, W. Jr., and Green, H. D.: Location of communications between cognate bed of descending ramus of left coronary and adjacent collateral vascular beds. Proc. Soc. Exper. Biol. & Med. **69:** 115, 1948.

[14] Carle, B. N., and Dewhirst, W. H.: A method for bleeding swine. J. Am. Vet. M. A. **101:** 495, 1942.

[15] Allen, J. B., and Laadt, J. R.: The effect of the level of the ligature on mortality following ligation of the circumflex coronary artery in the dog. Am. Heart J. **39:** 273, 1950.

[16] Gregg, D. E.: *loc. cit.*, P. 203.

[17] Fowler, W. M., Hurewitz, H. M., and Smith F. M.: The effect of theophyllin ethylendiamin on experimentally induced cardiac infarction in the dog. Arch. Int. Med. **56:** 1242, 1935.

Gold, H., Travell, J., and Modell, W.: The effect of theophylline with ethylendiamine (aminophylline) on the course of cardiac infarction following experimental coronary occlusion. Am. Heart J. **14:** 284, 1937.

[19] Mokatoff, R., and Katz, L. N.: The effect of theophyllin with ethylenediamine (aminophyllin) and of papaverine hydrochloride on experimental myocardial infarction in the dog. Am. Heart J. **30:** 215, 1945.

[20] Karsner, H. T., and Dwyer, J. E.: Studies in infarction. IV. Experimental bland infarction of the myocardium, myocardial regeneration and cicatrization. J. Med. Research **34** (NS 29): 21, 1916.

[21] Wiggers, C. J.: The functional importance of coronary collaterals. Circulation **5:** 609, 1952.

[22] Fisher, R. A.: Statistical Methods for Research Workers, ed. 11. London; Oliver and Boyd, 1950. Par. 21.02. The exact treatment of 2 x 2 tables. Pp. 96–97.

[23] Luykx, H. M. C.: Progress without Statistics. J.A.M.A. **141:** 195, 1949.

[24] Rabinovici, N., and Fine, J.: The effect of aureomycin on the intestine subjected to vascular injury. Ann. Surg. **135:** 344, 1952.

[25] Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: Multiple fresh coronary occlusions in patients with antecedent shock. Arch. Int. Med. **68:** 181, 1941.

[26] Master, A. M., Dack, S., Horn, H., Freedman, B. I., and Field, L. E.: Acute coronary insufficiency due to acute hemorrhage: An analysis of one hundred and three cases. Circulation **1:** 1302, 1950.

[27] Winsor, T., and Burch, G. E.: The electrocardiogram and cardiac state in active sickle cell anemia. Am. Heart J. **29:** 685, 1945.

Encephalomyocarditis

By OTTO SAPHIR, M.D.

Simultaneously occurring inflammations of the cerebrospinal system and myocardium are rare if one excludes poliomyelitis. The encephalomyocarditis virus and related strains have been shown to produce such lesions. Three instances in man are related and the reasons for a possible virus origin of this disease entity are given. A plea is made for virus studies in other pertinent cases.

THE PURPOSE of this study is to draw attention to a disease entity in man which resembles that observed by Schmidt,[7] and Schmidt and Helwig[6] in apes, mice and hamsters. We have observed three instances of this condition which only very rarely has been described in man. Though attempts to isolate an infectious agent, in particular a virus, were futile, it seems most likely that the disease was caused by a virus.

If one excludes poliomyelitis, information in regard to a virus which may cause both encephalitis and myocarditis in man is exceedingly scanty. Not only are there now a number of cases of poliomyelitis on record showing microscopic involvement of the myocardium with or without pertinent electrocardiographic changes, but also very recently Jungeblut and Edwards[1] were able to isolate poliomyelitis virus from both the spinal cord and the heart in two patients. Ungar[2] studied an instance of a diffuse interstitial myocarditis combined with epidemic encephalitis. Brenning[3] reported three clinical observations on encephalomyocarditis, stressing a rather sudden onset with marked anxiety, reflex disorders with or without involvement of cranial nerves, and simultaneous marked subjective heart troubles with more or less pronounced circulatory insufficiency. Richdorf[4] very recently was impressed with myocardial failure with brain involvement in children. He reported one instance of subacute encephalitis with electrocardiographic changes. Koch[5] very recently was able to demonstrate an infectious agent (virus) in the blood serum of one patient, in the cerebral spinal fluid of a second, and in the blood serum, feces, and liquid that was used to wash out an ear in the third. Neutralizing antibodies were found in the serum of those patients who recovered. This virus produced convulsions and paralysis in mice and rodents. Only one of these patients died. The autopsy showed an interstitial myocarditis, but the brain could not be examined. Koch[5] believes that this virus belongs to the encephalomyocarditis group of viruses.

Recently we had occasion to evaluate three instances of encephalomyocarditis. In spite of the fact that virus studies done on two of these patients were negative, it seemed important to relate these instances to underline the entity encephalomyocarditis and to stimulate virus studies on future cases. Only the most pertinent clinical and anatomic features of the cases shall be given.

CASE REPORTS

The first instance involves a 52 year old female who, 18 days before her death, developed severe headaches and abdominal distress.* When seen by a physician she was moderately confused and had difficulties in speaking. The following day she had a generalized convulsive seizure and auricular fibrillation, and two days later she became stuporous. On admission, she was lethargic and stuporous and responded only to very painful stimuli. The optic discs were flat and there was a 2 plus nuchal rigidity. The tendon reflexes were sluggish and the Babinski reflex could be elicited on the right side. The pupils reacted sluggishly to light. There was no apparent hemiplegia. A ventriculogram was normal. Her pulse rate varied between 101 and 166 beats per minute, but was most often about 130, and her

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This study was aided by the Ira Frank Fund.

This study has been presented before the First International Congress of Neuropathology in Rome, Italy, in September 1952.

* I am indebted to Dr. Paul C. Bucy for the clinical record.

temperature was between 101 and 104.6 F., most commonly being 102 F. Her arterial blood pressure fluctuated between 114/50 and 185/90. The spinal fluid pressure was increased to 260 mm.; it was clear, showed traces of globulin when subjected to Pandy's test and contained 30 cells, 50 per cent of which were lymphocytes and the rest polymorphonuclear leukocytes. The electrocardiogram* disclosed a rate of 150 per minute and a P-R interval of 0.12 second. The P waves were tall in leads II, III, and aV_F. The S-T segment was depressed in I; the T wave was flat in I. R was small in chest leads V_2 and V_4. S-T was depressed in V_6. T was notched in V_4, flat in V_6. There was sinus tachycardia, "P pulmonale," auricular premature systole in lead III, and horizontal position. The record was abnormal. However, the changes did not permit a specific diagnosis. Some of the chest lead abnormalities are seen with right ventricular dilatation.

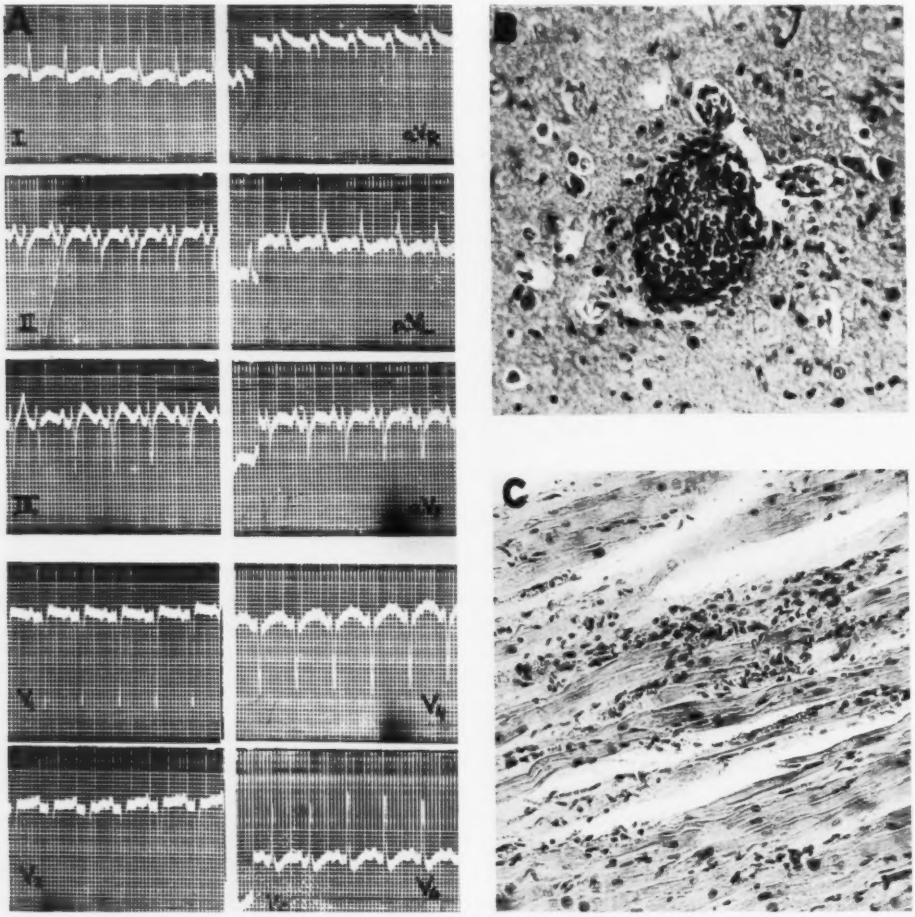

FIG. 1. *A*. Case 1. Electrocardiogram. (See text.) *B*. Case 1. Brain. Note the perivascular infiltration of round cells. Hematoxylin and eosin preparation. (×225.) *C*. Case 1. Myocardium. Note the necrotic muscle bundle and the cellular infiltration. Hematoxylin and eosin preparation. (×140.)

* I am grateful to Dr. R. Langendorf for the electrocardiograms.

Complement fixation tests for the St. Louis encephalitis, western equine encephalomyelitis, eastern equine encephalomyelitis, lymphocytic choriomeningitis, mumps and Japanese B encephalitis viruses and Q fever rickettsia were negative. Other laboratory tests were noncontributory.

During her stay at the hospital, she remained stuporous, gradually failing to react to any outside

timuli, and there were no spontaneous movements. The cardiac rate and respiration became very rapid and she died 13 days after admission.

At autopsy, the most important changes were found in the brain and the heart. The brain was larger and softer than normal. In particular, both temporal lobes were of very soft consistency, but, in addition, the medial surfaces of both frontal lobes just anterior to the corpus callosum and the subcallosal portions of the cerebral cortex were markedly involved and had a yellowish-pink appearance. The needle tracks in the posterior parietal regions were clearly noticeable. The basal ganglia appeared normal. On microscopic examination there were small and larger areas of perivascular hemorrhages in addition to many perivascular infiltrations of lymphocytes and mononuclear cells. Sections taken from the pons, medulla and cervical segment of the spinal cord also showed scattered foci of similar perivascular infiltrations. Many ganglion cells showed degenerative changes. Stains for bacteria gave negative results.

The heart weighed 350 Gm. and was greatly dilated. The valvular apparatus was intact. The myocardium was flabby and brown, tinged with yellow. There was flattening of the papillary muscles. In microscopic sections, the muscle fibers throughout were swollen and the intercalated discs appeared prominent. Accumulations of large mononuclear cells and lymphocytes were found in the interstitial tissues. In other fields, a few polymorphonuclear leukocytes were also encountered and there was much of an edema-like appearance in the interstitium. Small foci of muscle fibers appeared necrotic only in a few fields. These areas were surrounded by large mononuclear cells.

In the lungs were foci of bronchopneumonia with an early serofibrinous exudate in the pleura adjacent to the involved areas.

The main pertinent anatomic diagnosis was encephalomyocarditis.

The second case involved a 35 year old male.* The history and clinical course were extremely short. For about a week he had complained of severe headaches for which he took aspirin. When finally seen by a physician, he had a temperature of 101 F. but complained only of headache. He died unexpectedly shortly after the visit of the physician. At autopsy, the more important changes were again found in the heart and brain.

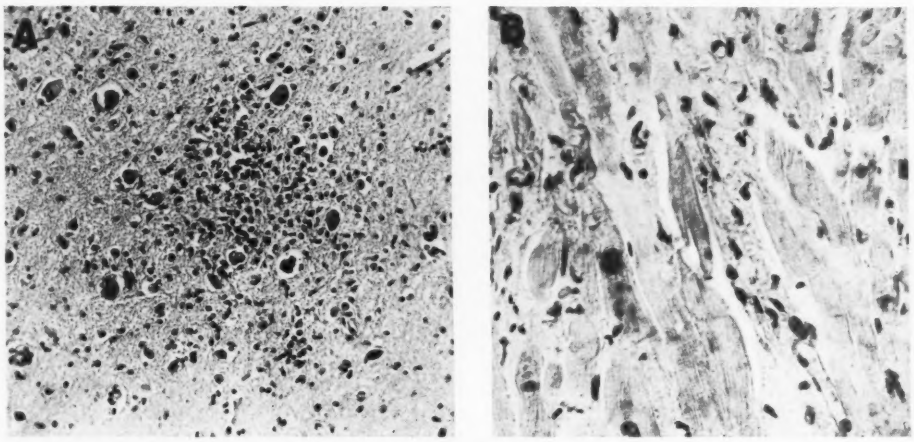

FIG. 2. *A*. Case 2. Brain. Note the degenerative changes in ganglion cells and focal infiltration of round cells and polymorphonuclear leukocytes. Hematoxylin and eosin preparation. (×140.) *B*. Case 2. Myocardium. Note the degeneration and necrosis of muscle fibers and a few inflammatory cells. Hematoxylin and eosin preparation. (×225.)

The brain was swollen, had a light pink tinge and was softer than normal. Multiple sections through the formalin-fixed brain only disclosed hyperemic vessels and a slightly pink color of the white substance. No hemorrhagic foci could be detected. On microscopic section, the Virchow-Robin spaces contained a liquid suspended in which were a few mononuclear cells. The smaller vessels themselves were engorged with red blood corpuscles and many lymphocytes and polymorphonuclear leukocytes were found in the periphery of their lumens. Rarely, small accumulations of polymorphonuclear cells and lymphocytes in groups were found, seemingly independent of vessels, throughout the white matter. The ganglion cells presented various degrees

* I am indebted to Dr. Max Berg for the clinical record.

of degenerative changes. Necrotizing lesions could not be made out and there was no proliferation of glia cells or fibers, or neuronophagia. There were no stainable microorganisms.

The heart weighed about 350 Gm.; it was slightly dilated. The pericardium was smooth; the mural endocardium and the valvular apparatus were intact. Neither the mouths of the coronary arteries nor these vessels themselves disclosed any noteworthy abnormalities. The papillary muscles were flattened and the myocardium was pale grayish-red, soft, flabby, and succulent. The course of the individual muscle bundles was obscured. Microscopically, the muscle fibers were swollen and their sarcoplasm was granular; the nuclei were often absent and small foci of necrosis were seen in a number of fibers. The interstitial tissue was edematous and there were small accumulations of lymphocytes with a few polymorphonuclear leukocytes scattered within the edema fluid. The capillaries and small vessels were dilated containing many red blood corpuscles and marginally placed polymorphonuclear leukocytes. Stains for bacteria gave negative results. Unfortunately, no attempts to isolate an etiologic virus by animal or chick embryo inoculation were made.

The pertinent anatomic diagnosis was acute myocarditis and acute encephalitis.

The third patient* was a 13 year old colored male who was admitted because of convulsions. He was well up to a week prior to admission when he developed a sore throat. Before admission he had chronic convulsions and swelling of the neck; he appeared lethargic. On admission he was comatose. His pulse rate was 160 plus, and he had a temperature of 105 F. The eyes reacted, if at all, only minimally. There was gallop rhythm. He was very restless, respirations were rapid, and he developed frequent coughing. He died seven hours after admission. The urine contained 4 plus albumin; the carbon dioxide combining power of the serum was 16 mM. per liter, and of the chlorides 111 mc. per liter. The total white count was 30,150; 84 per cent were polymorphonuclear leukocytes, many of which were nonsegmented; there were 15 lymphocytes and 1 monocyte. There were 3,640,000 red corpuscles. Spinal fluid was clear, containing three cells (lymphocytes). The Pandy test was negative. Spinal fluid glucose was found to be 101 mg. per 100 cc.

At autopsy, the more important changes were found in the brain, heart, lungs, and kidneys.

The brain was softer than normal and the gyri

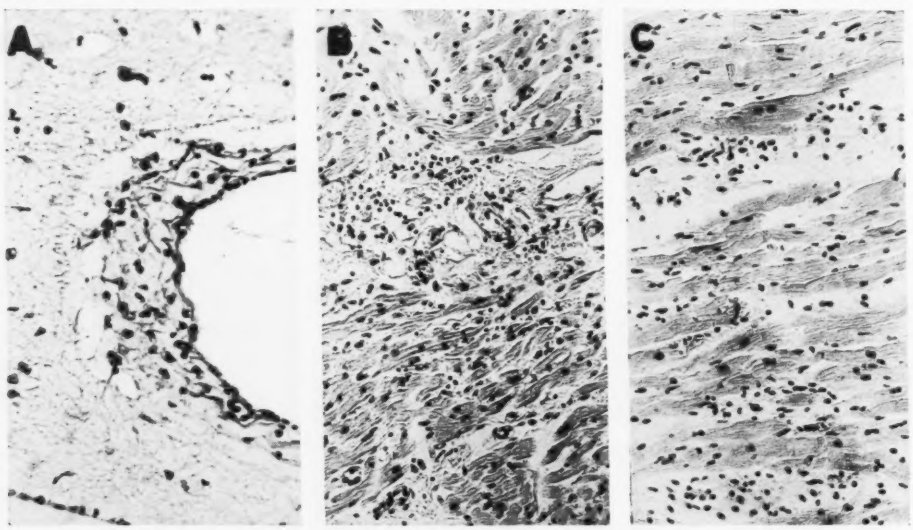

FIG. 3. *A*. Case 3. Brain. Note the perivascular infiltration of round cells and polymorphonuclear leukocytes. Hematoxylin and eosin preparation. (×220.) *B*. Case 3. Myocardium. Note the interstitial infiltration of round cells and a few polymorphonuclear leukocytes; also the severe degeneration of heart muscle fibers. Hematoxylin and eosin preparation. (×100.) *C*. Case 3. Myocardium. Note the diffuse infiltration of inflammatory cells and focal necrosis of muscle fibers. Hematoxylin and eosin preparation. (×140.)

* I am indebted to Dr. Joseph Calvin for the clinical record.

were flattened. On section, the smaller blood vessels were distended and the white matter was a little darker than normal with a slightly pink tinge. Microscopically, all the capillaries and small vessels were engorged with red blood corpuscles. This was particularly pronounced in the section taken from the wall of the third ventricle. The Virchow-Robin spaces often contained an edema-like material with a few polymorphonuclear leukocytes and an occasional lymphocyte. The ganglion cells throughout showed degenerative changes with absence of a number of nuclei. There was no neuronophagia. There were no bacteria.

The heart was enlarged and dilated, weighing 260 Gm. instead of about 150 Gm., as is usual for a 13 year old boy. There were subepicardial hemorrhages along the base. The mural and valvular endocardium were intact. The myocardium was softer than normal, pale, with small reddish areas scattered through it. The coronary arteries were normal. Microscopically, much of an edema-like material was found in the interstitial tissue with many polymorphonuclear leukocytes, lymphocytes and a small number of endothelial leukocytes. Deposition of fibrin was also noted. The muscle fibers were slightly swollen, but their striations appeared distinct. There were foci of necrosis. Stain for bacteria gave negative results.

The vascular markings of the lungs were more pronounced than normal, indicative of dilatation of the lymph channels. From the section made by cutting, a very large amount of frothy fluid exuded. Microscopically, in addition to the edema, a hyalin-like pink membrane was found lining the inner wall of some alveoli. These and other alveoli contained monocytes and a few lymphocytes. The interstitial tissue throughout was richly infiltrated by lymphocytes and endothelial leukocytes.

The kidneys were enlarged and soft. Many punctate foci of hyperemia and minute hemorrhages were encountered. The architecture of the cortex was obscured. It was grayish and riddled with red dots. The pyramids were hyperemic. Microscopically, small numbers of polymorphonuclear leukocytes were seen between capillary loops of the glomeruli.

The pertinent anatomic diagnosis was acute encephalitis, acute, principally interstitial, myocarditis, interstitial pneumonia, and acute intercapillary glomerulonephritis.

The heart was ground in a sterile mortar with alundum and suspended in nutrient broth. The suspension was injected both intracerebrally and intraperitoneally into albino Swiss mice.* None of the animals developed any pathologic lesions.

Discussion

All three patients had myocarditis and encephalitis. The course of the disease in two of these patients was rapid, one dying after only eight hours hospitalization and the other at home after a short history of headache and fever. The first patient was hospitalized 13 days prior to her death.

The course of two of these patients resembled that of the chimpanzees reported by Helwig and Schmidt,[6] and by Schmidt.[7] Because of the interest the studies of these authors created in the concept of encephalomyocarditis, their work and related studies may be mentioned in a little more detail. Helwig and Schmidt[6] found in a male gibbon and a 5 year old male chimpanzee, who had died suddenly, a diffuse interstitial myocarditis, bilateral hydrothorax and pulmonary edema. The brain showed no changes and the spinal cord was not examined. Fluid from the chest cavity of the chimpanzee and the spleen, suspended in saline solution, was inoculated into five mice each. All of these mice developed paralysis of the hind legs and showed microscopically widespread myocarditis. Hen eggs were inoculated with 10 per cent serum-saline suspension of two mouse hearts from a third passage of the original ape-chest fluid which had previously been passed through a Seitz filter. These eggs were opened on the third day after inoculation and the markedly hyperemic embryos and membranes were frozen. Later, these were suspended in ascitic fluid, ground, and passed through a Berkefeld filter. This sterile filtrate consistently produced myocarditis in 31 mice and in 8 out of 11 guinea pigs that were inoculated. Helwig and Schmidt[6] believed that the cardiac lesions of this ape disease and sporadic human acute interstitial myocarditis of unknown etiology were strikingly similar. In 1948 Schmidt[7] found a similar type of myocarditis in a 6 year old female chimpanzee which had apparently been ill for five days with edema of the face, subnormal temperature and dysphagia. Terminally cyanosis and dyspnea developed. In addition to myocarditis, hydrothorax and a marked hemorrhagic pulmonary edema were present. Schmidt,[7] using the etiologic agent recovered from the 5 year old male chimpanzee, was able to produce myocarditis and encephalitis in mice and hamsters and myocarditis in guinea pigs. This agent

* Virus work was done by Dr. A. Milzer.

which behaved like a virus had not been identified with any of a variety of known viruses by various biologic tests. Warren and Smadel[8] who studied this agent found that it became highly neurotropic when maintained by a serial intracerebral passage in mice. Encephalitis developed rapidly and mice died within 24 hours. While no microscopic evidence of myocarditis was found in mice dying rapidly, an extensive acute focal necrotizing myocarditis, recognizable grossly, occurred when death was delayed. Histologic changes in the brain were characterized by widespread necrosis of nerve cells when death occurred early, and by an extensive cellular infiltration after a protracted disease. Hamsters also developed encephalitis and myocarditis after inoculation of this virus. Warren and Smadel[8] named the virus "encephalomyocarditis (EMC)" virus.

Studying the encephalomyocarditis virus further, Warren, Smadel and Russ[9] found that Columbia SK and the MM virus exhibited cross neutralization with the encephalomyocarditis virus. Dick's[10] experiments indicate that the meningoencephalitis, Columbia SK, the MM virus and the encephalomyocarditis virus were closely related serologically, in their pathogenicity and in their pathologic effect in experimentally infected small animals. Warren, Smadel and Russ[9] stated that neutralization, complement fixation and cross immunity tests, indicated that these four viruses were identical and that they may be regarded as probably different strains of a single virus. Reiman[11] concluded that all four members of this group may cause myocardial lesions. During studies to determine the relation of the encephalomyocarditis virus to disease in man, Smadel and Warren[12] found that neutralizing antibodies appeared in the sera of a group of American soldiers recuperating from a short febrile illness contracted in the Philippines. The disease was characterized by a moderately high fever, severe headache accompanied by a stiff neck, positive Kernig's sign, hyperactive reflexes and pharyngitis. There were from 50 to 500 cells, mainly lymphocytes in the spinal fluid. The fever lasted only for two or three days and all patients were discharged from the hospital within four or five days. There were no sequelae. Interesting also, in respect to the foregoing, is Warren's[13] finding that convalescent serum from a human case of meningoencephalomyelitis neutralized more than 1,000 50 per cent lethal doses of encephalomyocarditis virus (quoted by Dick[10]). Warren, Russ and Jeffries[14] found neutralizing antibodies against the group of viruses in sera from an appreciable number of 442 wild rats trapped in several widely separated areas of the United States.

From this short report, it is clear that there are viruses, or several strains of a virus—excluding the virus of poliomyelitis—capable under certain circumstances, of causing principally encephalitis and myocarditis in laboratory animals.

All three patients whom we have studied here had the type of encephalitis usually ascribed to virus origin. A clinical diagnosis of encephalitis was made in the first and third instances, but not made in the second, the patient having died at home. Myocarditis was diagnosed clinically in only one case, but was found at autopsy in all three. Though morphologically the myocarditis, per se, is not characteristic in these instances, it resembles that seen in certain stages of poliomyelitis and also in the two chimpanzees observed by Helwig and Schmidt,[6] and by Schmidt.[7] An interesting coincidence is also the finding of the edema of the face in both the 13 year old boy of this study and the second chimpanzee, though this was explained in our case on the basis of the glomerulonephritis. The interstitial pneumonia with the characteristic exudate and the presence of the hyaline-like inner rim within the alveoli is also considered of virus origin. The serum of the first patient gave negative complement fixation tests for the St. Louis encephalitis, western equine encephalomyelitis, eastern equine encephalomyelitis, lymphocytic choriomeningitis, mumps and Japanese B encephalitis viruses and Q fever rickettsia. No other virus studies were made. Though looked for, no agent could be demonstrated in the heart muscle of the third case.

In all these cases foci of necrosis of heart muscle fibers were encountered. Rustigian and Pappenheimer[15] were impressed by muscle necrosis with acute inflammatory changes produced by Jungeblut's SK virus. Such changes

were also encountered following introduction of other encephalomyelitis virus strains. Melnick and Godman[16] described muscle necrosis in mice as a result of inoculation with the Conn.-5 strain of Coxsackie virus. This was followed by inflammatory lesions. Myocardial necrosis also occurred in mice, but to a lesser degree. In the light of these experimental findings, the foci of necrosis of the myocardium in our cases may be significant. Skeletal muscles, however, were not examined. It might be possible that these strains of viruses produce necrosis of muscles throughout the body, involving also the heart muscle. It is because of the latter, however, that the patients succumb so quickly.

From the foregoing, in spite of inability to demonstrate a virus, it seems likely that both the encephalitis and myocarditis were caused by a virus. From the similarity of the clinical picture and the microscopic findings, it is most likely that the cause of the encephalomyocarditis in these three patients is similar to that recovered from the original chimpanzee, the encephalomyocarditis virus, or, perhaps better, the virus whose different strains may constitute the encephalomyocarditis, Columbia SK, MM and meningoencephalitis viruses.

Schmidt[7] suggested that "isolated myocarditis" as described by Fiedler[17] may be caused by a similar virus, since, as stated before, the virus in certain animals may produce myocarditis only. Fiedler,[17] in his original communication, reported four instances. The microscopic appearance of these hearts as studied by Schmorl was not uniform, though the interstitial character of the inflammation was stressed in at least three of these cases. It is of interest to note that one patient among these three studied by Fiedler (case 3) in addition to presenting signs of myocarditis also suffered from convulsions which started two days before she died. These were described as very severe and recurring frequently. Myocarditis was found at autopsy and areas of necrosis were described histologically. The brain was not examined. It is possible that this case of the original Fiedler's series might actually have been caused by a virus of the encephalomyocarditis group.

If, thus, attention is focused on an entity of inflammatory lesion of the brain and myocardium it would seem from the studies of Brenning,[3] Richdorf,[4] Koch[5] and from our report that encephalomyocarditis perhaps is not a rare entity. Whenever such a disease complex is considered clinically, it is imperative that the serum be examined for neutralizing antibodies involving the virus of encephalomyocarditis, the meningoencephalitis virus, the Columbia SK and MM viruses. At autopsy, an attempt should be made to isolate the virus from the heart and brain by the inoculation of mice, hamsters, or the chick embryo.

Summary

A clinical and pathologic entity—encephalomyocarditis—is described. The literature is reviewed and pertinent studies on experimental viruses are invoked for an understanding of this entity. This disease may be characterized by clinically recognizable evidence of severe encephalitis combined with electrocardiographic changes indicating myocardial damage and, often, unexpected death; or the involvement of either brain or myocardium may not be recognized clinically until convulsions and coma appear, followed by unexpected death. Three such instances are reviewed. Whenever such a disease complex is considered clinically, it is imperative that the serum be examined for neutralizing antibodies involving the viruses of encephalomyocarditis, the meningoencephalitis virus, the Columbia SK and MM viruses. At autopsy, an attempt should be made to isolate the virus from the heart and brain by the inoculation of mice, hamsters or the chick embryo.

REFERENCES

[1] Jungeblut, C. W., and Edwards, J. E.: Isolation of poliomyelitis virus from the heart in fatal cases. Am. J. Path. **21:** 601–623, 1951.

[2] Ungar, H.: Diffuse interstitial myocarditis in a case of epidemic encephalitis. Am. J. Clin. Path. **18:** 48–54, 1948.

[3] Brenning, R.: Encephalomyocarditis acuta—a disease sui-generis? Acta Soc. med. upsalien., **56:** 51–58, 1951.

[4] Richdorf, L. F.: Myocardial failure in children with brain involvement. J. Lancet **70:** 166–170, 1950.

[5] Koch, F.: Die Encephalomyocarditis (EMC) und ihre Abgrenzung von der Polyomyelitis. Ztschr. Kinderh. **68:** 328–357, 1950.

[6] HELWIG, F. C., AND SCHMIDT, E. C. H.: Passing agent producing interstitial myocarditis in anthropoid apes and small animals. Science **102:** 29–31, 1945.

[7] SCHMIDT, E. C. H.: Virus myocarditis. Pathologic and experimental studies. Am. J. Path. 99–118, 1948.

[8] WARREN, J., AND SMADEL, J. E.: Further observations on the virus of encephalomyocarditis. J. Bact. **51:** 615–616, 1946 (Sc. Proc. 46th meeting of Soc. Am. Bact., Detroit, May 21–24, 1946.)

[9] —, —, AND RUSS, S. B.: The family relationship of EMC, Columbia SK, MM and meningoencephalitis, myelitis viruses. J. Immunol. **62:** 387–398, 1949.

[10] DICK, G. W. A.: The relationship of meningoencephalitis, encephalomyocarditis, Columbia SK and MM viruses. J. Immunol. **62:** 375–386, 1949.

[11] REIMAN, H. A.: Infectious diseases. Arch. Int. Med. **87:** 128–174, 1951.

[12] SMADEL, J. E., AND WARREN, J.: The virus of encephalomyocarditis and its apparent causation of disease in man. J. Clin. Investigation **26:** 1197, 1947.

[13] WARREN, J.: Quoted by Dick, G. W. A.

[14] —, RUSS, S. B., AND JEFFRIS, H.: Neutralizing antibody against viruses of the encephalomyocarditis group in the sera of wild rats. Proc. Soc. Exper. Biol. & Med. **71:** 376–378, 1949.

[15] RUSTIGIAN, R., AND PAPPENHEIMER, A. M.: Myositis in mice following intramuscular injection of viruses of the mouse encephalomyelitis group and of certain other neurotropic viruses. J. Exper. Med. **89:** 69–92, 1949.

[16] MELNICK, J. L., AND GODMAN, G. C.: Pathogenesis of Coxsackie virus infection. J. Exper. Med. **93:** 247–266, 1951.

[17] FIEDLER, A.: Über akute interstitelle Myokarditis. Festschrift zur Feier des 50 jähr. Bestehens des Stadtkrankenhauses zu Dresden-Friedrichstadt. **2:** 3–24, 1899.

The Intestinal Excretion of Digitoxin in the Rat

By SHIRLEY ST. GEORGE, PH.D., AND MEYER FRIEDMAN, M.D.

Rats given a parenteral injection of digitoxin (1 μg. per gram of body weight) were found to excrete approximately 15 to 18 per cent of the dose in their feces. This fecal digitoxin however came from the bile, and there was no evidence of any active secretion of the glycoside by the bowel wall itself.

FOR MANY YEARS workers[1, 2] have commented on the high degree of insensitivity to the toxic effects of the cardiac glycosides shown by rats and mice. Nevertheless, general speculation on whether this insensitivity was due to an extraordinarily effective excretion of the active cardiotonic principle or to rapid destruction of the drug within the body could not be resolved because of the limitations imposed by the quantitative technics available. Recently, however, we have been able to study by means of the microsensitive embryo duck heart preparation,[3] the renal role[4] in the excretion of digitoxin. Here we shall complete the study of the possible excretion of this drug by communicating our findings on the intestinal excretion of cardioactive digitoxin or its aglycone.

METHODS

Twenty-one male adult rats of the Long-Evans strain were given digitoxin (1.0 microgram per gram of body weight) by intravenous injection. They were placed in the Bollman[5] type of restraining cage and the feces were collected on 17 rats the first 24 hours, on 11 during the second as well as the first 24 hour period, on eight during the third and fourth as well as the first and second days. Five additional rats were injected in the same manner after a biliary fistula had been produced in each of them. Their stools and bile were collected for 24 hours.

The feces collected during any 24-hour period were dried 24 hours in vacuo at 70 C., then macerated in a Waring blender in 75 ml. of cold ethyl ether and 1.0 Gm. of diatomaceous earth for approximately two minutes. This suspension was filtered and the filtrate evaporated to dryness. The residue then was taken up in Tyrode's solution, and assayed for its digitoxin content by the embryonic duck heart preparation.[3] A standard recovery curve was prepared by adding known quantities of digitoxin to samples of rat feces (5 Gm.) and extracted precisely as outlined above for the experimental series. The presence of as little as 2 micrograms of digitoxin in a 5 Gm. sample of feces could be detected by this method. Bile samples were assayed according to a previously described method.[6]

FINDINGS AND DISCUSSION

It is apparent from the data in table 1 that a small but significant[1] fraction (6 per cent) of digitoxin finds its way into the gut of the rat during the first 24 hours after parenchymal injection of the drug. The excretion during the second day, moreover, is about the same as that of the first but a fall occurs the third day and by the fourth day, no digitoxin could be detected in the stool of any injected rat.

In view of the fact that in a previous study,[6] we found that the rat excreted about the same amount of digitoxin in his daily bile as we now found in his stools, the question arose as to the possibility that the digitoxin detected in the stools of the injected rats might have been brought there via bile. An assay of the stools and bile of five injected rats indicated that this was the actual state of affairs. Thus (see table 1), the stools of these five rats were found to contain no digitoxin although their bile contained an average of 13 micrograms of digitoxin or about 6 per cent of the administered dose (the same increment of the total given as that observed in the stools of the intact rats above). It also follows from the similar quantity ex-

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Aided by grants from The Life Insurance Medical Research Fund, Eli Lilly and Co., and the United States Public Health Service.

TABLE 1.—*The Intestinal Excretion of Digitoxin by the Rat after the Injection of One Microgram per Gram Body Weight*

Rat No.	Digitoxin Injected (μg.)	Digitoxin in Feces (μg.) 0–24 Hrs.	24–48 Hrs.	48–72 Hrs.	72–96 Hrs.	Digitoxin in Bile (μg.) 0–24 Hrs.
A. Intact Rats						
I-1	191	20	—*	—	—	—
I-2	240	20	—	—	—	—
I-3	208	10	—	—	—	—
I-4	230	20	—	—	—	—
I-5	230	30	—	—	—	—
II-1	268	20	10	—	—	—
II-2	252	40	10	—	—	—
II-3	272	10	20	—	—	—
II-4	248	10	10	—	—	—
II-5	270	10	10	—	—	—
II-6	289	20	10	—	—	—
II-7	273	10	10	—	—	—
II-8	276	10	—	—	—	—
III 1	280	10	10	10	0*	—
III-2	222	10	20	0	0	—
III-3	222	10	5	5	0	—
III-4	216	10	20	5	0	—
IV-6	190	—	—	10	0	—
IV-7	224	—	—	10	0	—
IV-8	188	—	—	10	0	—
IV-9	224	—	—	10	0	—
Average		15	12	7	0	—
Per Cent Excreted		6	5	3	0	—
B. Rats with Biliary Fistula						
V-2	220	0	—	—	—	12
V-3	207	0	—	—	—	8
V-4	220	0	—	—	—	15
V-5	266	0	—	—	—	17
V-6	182	0	—	—	—	14
Average		0	—	—	—	13
Per Cent Excreted		0	—	—	—	6

* A dash (—) indicates that no tests were done. A zero (0) indicates that tests were done but no digitoxin found.

creted in bile and appearing in feces in a given time period, that there is very little resorption of biliary excreted digitoxin through the gut wall.

These results when added to those obtained previously on the renal excretion of digitoxin in rats[4] suggest that no more than 20 per cent of a given dose of digitoxin will be excreted in the stool or urine of the rat. Approximately 15 to 18 per cent of this amount will be found in the stools. It seems therefore that the rat manages to destroy, not excrete, the major portion of a given dose of digitoxin. He differs in this respect quite considerably from man.

SUMMARY

Significant quantities of digitoxin are excreted into the bowel after parenchymal administration of the drug. Bile was found to be the route of this intestinal conveyance of the drug.

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REFERENCES

[1] GOTTLIEB, R.: Über die Aufnahme der Digitalissubstanzen in der Gewebe. Arch. exper. Path. u. Pharmakol. **82:** 1, 1917.

[2] WEESE, H.: Digitalis. Leipzig, Georg Thieme, 1936.

[3] FRIEDMAN, M., BINE, R., JR., AND BYERS, S. O.: Urinary excretion of digitoxin in the rat. Proc. Soc. Exper. Biol. & Med. **71:** 406, 1949.

[4] FRIEDMAN, M., AND BINE, R., JR.: Employment of the embryonic duck heart for the detection of minute amounts of a digitalis glycoside (Lanatoside C) Proc. Soc. Exper. Biol. & Med. **64:** 162, 1947.

[5] BOLLMAN, J. L.: A cage which limits the activity of rats. J. Lab. & Clin. Med. **33:** 1348, 1948.

[6] ST. GEORGE, S., BINE, R., JR., AND FRIEDMAN, M.: Role of the liver in excretion and destruction of digitoxin. Circulation **6:** 661, 1952.

The Renal Excretion of Digitoxin in the Acute and Chronic Cardiac Patient

By MEYER FRIEDMAN, M.D., SHIRLEY ST. GEORGE, PH.D., RENÉ BINE, JR., M.D., AND SANFORD O. BYERS, PH.D.

The renal excretion of digitoxin was studied in cardiac patients who were (1) decompensated and (2) compensated. It was found that the renal excretion of digitoxin was not changed in patients suffering from left ventricular failure alone but diminished considerably during the first 24 hours of decompensation in patients suffering from both right and left ventricular failure. Patients who were maintained in a good state of compensation by adequate digitalization were found to excrete 30 to 40 per cent of their daily dose of digitoxin. Patients overdigitalized were found to excrete 70 or more micrograms of digitoxin a day. The maximal amount of digitoxin able to be destroyed in the body was considered to be approximately 50 μg. per day, a finding which explains why dosages in excess of 0.15 mg. almost invariably lead to overdigitalization.

RECENTLY, we have been able to determine in a direct, quantitative fashion the renal excretion of digitoxin in the rat,[1] rabbit and dog,[2] and in normal man.[3] The results left little doubt that the normal *young* adult, unlike the animals studied, excreted a considerable fraction (approximately 40 per cent) of administered digitoxin in his urine. The individual over 60 years of age on the other hand, was found to excrete digitoxin poorly, at least during the first 24 hours following its administration.

These observations, however, did not yield any information concerning the renal excretion of the glycoside by the *cardiac* patient either (1) when he was decompensated, or (2) when he was being maintained in a state of compensation by administration of digitoxin. Renal studies, therefore, were done on such patients and the results of these studies are presented below.

METHODS

A. *Selection of Subjects and Patients*

1) *Normal Subjects.* Nine normal middle-aged subjects (37 to 66 years) were picked purposely in order that the control data would be obtained on subjects whose age was similar to that of the cardiac patients. These patients were given 1.2 mg. of digitoxin (either by mouth or by vein) within a period of six hours. Urine was collected daily for three consecutive days. Each sample was assayed separately.

2) *Patients in Acute Cardiac Decompensation.* Eight patients suffering from acute left ventricular failure, and eight from both left and right ventricular failure were given 1.2 mg. of digitoxin (Crystodigin) either orally or parenterally within a period of six hours and the total daily urine was collected when possible for three days. None of these patients had been taking digitalis or one of its glycosides before.

Patients suffering from acute left ventricular failure were chosen for this study if, besides the presence of organic heart disease, they suffered from (1) dyspnea, tachypnea, orthopnea, at least one attack of pulmonary edema, and (2) prolongation of circulation time (arm to tongue), an accentuated pulmonic second sound and basal pulmonary rales. Right ventricular failure was considered to be present in those patients who exhibited signs of increased venous pressure, hepatomegaly, or an accumulation of extravascular fluid in the tissues or in the pleural or peritoneal cavities.

3) *Compensated Cardiac Patients.* A urine collection of 24 hours was made on 18 cardiac patients each of whom previously had suffered from one or more bouts of congestive failure but who had been maintained in a state of compensation by adequate digitoxin therapy (0.1 to 0.15 mg. per day) for periods varying from 2 to 60 months preceding our studies. A patient was considered adequately digitalized and well compensated if there were no indications of excess extravascular fluid, increasing dyspnea or orthopnea, tachycardia, or pulse deficit. The electrocardiograms of almost all of these patients exhibited some depression of the S-T segment in the limb leads indicative of medication with the digitalis glycoside.

A urine collection also was made on four chronic cardiac patients at the time they exhibited signs and symptoms of overdosage with digitoxin.

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Aided by grants from the Life Insurance Medical Research Fund, Eli Lilly and Company, and the United States Public Health Service.

TABLE 1.—*The Renal Excretion of Digitoxin in Digitalized† Patients Suffering from Acute Cardiac Failure*

Name	Age (Years)	Diagnosis	Urine (0–24 Hours)			Urine (24–48 Hours)			Urine (48–72 Hours)		
			Volume (cc.)	Digitoxin (μg)	Per Cent Excreted	Volume (cc.)	Digitoxin (μg)	Per Cent Excreted	Volume (cc.)	Digitoxin (μg)	Per Cent Excreted
A. Control Normal Subjects											
MF	41	No Disease	1290	39	3.2	1155	46	3.8	1550	47	3.9
AR*	50		2800	84	7.0	1420	21	1.8	2420	24	2.0
MD(F)	66		2050	62	5.2	810	12	1.0	—	—	—
WAM*	50		1710	34	2.8	1120	45	3.8	1120	34	2.8
EM	37		1080	32	2.7	1080	32	2.7	—	—	—
VF*	42		1335	40	3.3	—	—	—	—	—	—
GW	41		980	20	1.7	1040	50	4.2	1340	33	2.8
MS(F)	64		1150	46	3.8	1300	26	2.2	1490	30	2.5
SS*	40		1240	40	3.3	2380	80	6.7	1620	62	5.2
Average	48		1426	44	3.7	1288	39	3.3	1590	38	3.2
S.E. Mean				±5.8			±7.0			±5.1	
B. Patients in Left Ventricular Failure											
IM	63	CAD	2115	42	3.5	1820	54	4.5	620	12	1.0
AR	45	CAD	1800	27	2.3	1380	28	2.3	—	—	—
HR	56	CAD	1800	36	3.0	2200	24	2.0	—	—	—
MJ	65	CAD	2000	60	5.0	1470	27	2.3	2170	32	2.7
NA*	42	HHD	1390	25	2.1	1600	12	1.0	1900	76	6.3
RG*(F)	64	HHD	2390	26	2.2	2150	80	6.7	1160	23	1.9
SJ*(F)	38	HHD	1240	42	3.5	2380	83	6.9	1600	64	5.3
VS*(F)	46	HHD	1240	50	4.2	1200	30	2.5	1940	68	5.7
Average	52		1747	39	3.2	1775	42	3.5	1565	46	3.8
S.E. Mean				±4.1			±8.8			±10.0	
C. Patients in Left and Right Ventricular Failure											
PR	44	RHD-MS	920	28	2.3	—	—	—	—	—	—
RA	40	RHD-MI(AF)	1000	15	1.3	—	—	—	—	—	—
RG	63	CAD	1320	13	1.1	1520	46	3.8	—	—	—
HE*(F)	60	CAD	925	23	1.9	1770	44	3.7	1680	34	2.8
HA*(F)	63	CAD	2000	28	2.3	—	—	—	—	—	—
RN	50	HHD	820	21	1.8	950	15	1.3	480	22	1.8
PH*	46	HHD	820	16	1.3	—	—	—	1730	58	4.8
MD*	61	RHD-AS-AI	1120	8	0.7	—	—	—	—	—	—
Average	53		1116	19	1.6	1413	35	2.9	1293	38	3.1
S.E. Mean				±2.4							

* Digitoxin given by intravenous injection.

† Each patient given 1.2 mg. of digitoxin either orally or intravenously.

(F): Female

CAD: Coronary Artery Disease
HHD: Hypertensive Heart Disease
RHD: Rheumatic Heart Disease
MS: Mitral Stenosis
MI: Mitral Insufficiency
AS: Aortic Stenosis
AI: Aortic Insufficiency
AF: Auricular Fibrillation

B. Assay of Digitoxin in Urine

The digitoxin content of the daily urine was determined by previously described methods.[3] Briefly, this process consisted of extracting known amounts of added digitoxin (1 to 12 micrograms) from fixed quantities of urine (200 cc.), brought to a standard specific gravity of 1.015. The final extracts were dissolved in Tyrode's solution (50 cc.). The Tyrode's solution was warmed to, and maintained at, 33 C. and then six or more embryonic duck hearts were added. The average time at which the "digitalis effect"[1] occurred in these hearts was noted for each extraction. Thus, for example, a series of 15 extracts of 200 cc. quantities of urine originally containing 2 micrograms of digitoxin were observed to produce a "digitalis effect" in a period of 47 minutes (standard error of mean: ±2.3 minutes); whereas 10 extracts of 10 different urine samples containing 4 micrograms produced a "digitalis effect" in 27 minutes (standard error of mean: ±1.5 minutes).

After standards for various quantities of digitoxin in urine had been established in this manner, 200 cc. samples of urine containing an unknown amount of digitoxin could be extracted and assayed by comparing the results obtained with those previously obtained from the standard known values. The total daily excretion then was calculated by multiplying the amount of digitoxin found in the 200 cc. quantity of urine by the total daily urine volume/200. Urines which were too dilute or too concentrated were adjusted by evaporation or dilution respectively until a 200 cc. quantity had a specific gravity of 1.015 before the extraction process itself was begun.

TABLE 2.—*The Renal Excretion of Digitoxin in Chronic Digitalized Cardiac Patients*

	Name	Age (Years)	Diagnosis	Digitoxin Given/Day (mg.)	Duration of Treatment (Months)	Urine/Day		
						Volume (cc.)	Digitoxin (μg)	Per Cent Excreted
			A. Patients Adequately Digitalized					
1)	MT	60	RHD-AI	0.1	2	2620	52	52
2)	SJ	48	CAD	0.1	24	1340	54	54
3)	SH(F)	41	RHD-MS-MI	0.15	3	1720	48	32
4)	EA(F)	39	HHD	0.15	2	1300	33	22
5)	WW	41	CAD	0.15	4	845	42	28
6)	VS	48	HHD	0.10	3	1950	34	34
7)	RT(F)	39	RHD-MS-MI-(AF)	0.15	26	1370	54	36
8)	LM(F)	46	RHD-MS-MI-(AF)	0.10	24	1040	26	26
9)	RJ	68	CAD	0.10	24	1520	43	43
10)	SW(F)	53	HHD	0.10	48	830	21	21
11)	WF	53	CAD-(AF)	0.10	60	1870	56	56
12)	FC	39	RHD-AI	0.15	2	1610	56	37
13)	SJ	39	HHD	0.10	2	860	40	40
14)	OO	56	CAD	0.10	36	660	36	36
15)	JB	64	RHD-AS-(AF)	0.10	60	1710	34	34
16)	RW(F)	55	CAD	0.10	12	850	30	30
17)	RB	36	RHD-MI-(AF)	0.10	48	810	36	36
18)	MD	34	RHD-MI-AI	0.10	48	1400	35	35
Average		47		0.12	24	1350	41	36
S.E. Mean							±2.3	
			B. Patients Exhibiting Signs of Overdigitalization					
1)	WM	50	CAD	0.15	4	2000	89	59
2)	RL	69	RHD-AS	0.40	1	1800	120	30
3)	JD(F)	40	RHD-MS	0.20	12	1400	70	35
4)	JDK	58	CAD	0.60	1	2630	115	19
Average		54		0.34	5	1956	99	36

RESULTS

A. Patients in Acute Failure

1) *Left Ventricular Failure.* Renal excretion of digitoxin was not diminished in patients

suffering from acute left ventricular failure. The average urinary excretion in eight patients during the first three days after *either* oral or parenteral administration of 1.2 mg. of digitoxin was 39, 42, and 46 micrograms per day, respectively. As table 1 illustrates, this daily rate of excretion (about 3 per cent of the total dose) was approximately the same as that found in the control subjects. It is of interest too, that renal excretion of the glycoside was as extensive after oral as after parenteral administration of the drug.

2) *Left and Right Ventricular Failure.* Apparently the onset of right ventricular failure markedly diminished renal excretion of digitoxin for at least the first 24 hours after administration of the drug. Thus (see table 1), the average renal excretion in eight patients suffering from both right and left ventricular failure was only 19 micrograms (1.6 per cent of administered dose) during the first 24 hours. However, after the first day, the average renal excretion increased so that at the end of the third day, the renal excretion of digitoxin in the three patients studied was about equal to that of the patient with left ventricular failure or the normal subject.

B. Compensated Cardiac Patients

Chronic cardiac patients whose compensation was being maintained by administration of digitoxin were found (see table 2) to excrete an average of 41 micrograms of digitoxin (range: 21 to 56 micrograms) in their urine per day. This amount represented approximately 36 per cent (range: 21 to 56 per cent) of their average daily dose (0.12 mg.) of digitoxin.

Four patients who exhibited signs of overdosage with digitoxin excreted over twice as much digitoxin (average: 99 micrograms) in their daily urine.

Discussion

The above results suggest that the cardiac patient suffering from acute left ventricular failure excretes digitoxin in his urine as well, and in as great an amount, as the normal subject. Moreover, the renal rate is the same whether the drug is given by mouth or vein suggesting that there is probably complete gastrointestinal absorption of the drug.

On the other hand, a patient with combined right and left ventricular failure, is not able to excrete as much administered digitoxin during the first 24 hours as the normal subject. Whether this is due to some type of renal dysfunction secondary to venous congestion or to a greater escape of digitoxin in swollen extravascular compartments was not determined. The observed decrease in excretion, however, was of brief duration and after 24 hours, digitoxin was excreted in normal quantities. It is our opinion that this resumption of a normal rate of renal excretion of the glycoside was associated with the advent of diuresis.

The cardiac patient who was maintained in a state of compensation by the daily ingestion of digitoxin, excreted just about the same amount of glycoside (41 micrograms) as the normal individual (who was given the same amount of digitoxin) was found[3] to do. The cardiac patient, similar again to the normal individual, exhibited an excess of digitoxin in his urine (70 or more micrograms per day) whenever he exhibited clinical signs of overdosage with the drug. Using this urinary assay, we have been able to determine whether adequate or excessive digitalization existed in doubtful cases. Such assays proved to be very accurate as judged by later clinical observation.

It is of interest that the patient does not appear to excrete a maximum fraction of administered digitoxin until after about 1.2 mg. of the drug ostensibly has been accumulated in his tissues. Thus, only about 3 to 5 per cent of an initial dose of digitoxin (regardless of whether 0.2 or 1.2 mg. is given[3]) is excreted in the first day's urine. However, if after an initial dose of 1.2 mg. has been given, the patient or subject is maintained on 0.1 mg. or more per day, 30 to 40 per cent of this daily dose is excreted in the daily urine. This fraction appears to represent the maximum capacity of the kidney to rid the body of digitoxin. Thus, although an average of 99 micrograms of digitoxin was found in the daily urines of our four toxic patients, this still represented only 36 per cent of the average amount of the drug given to these patients. This fraction then appears

fixed when relatively moderate quantities of digitoxin are given to a digitalized patient but whether this same fraction of a much larger dose also would be excreted by the kidney cannot be answered by our present data.

The fraction of digitoxin not excreted by the kidney (60 to 70 per cent of a given dose) is either excreted in the bile or destroyed in the body. An earlier study[4] has indicated that not more than 10 per cent of a given dose is excreted in the bile of man. Therefore, the body apparently can destroy about 50 per cent of a daily dose of 0.1 mg. of digitoxin (about 50 micrograms per day). This appears to be about the maximal capacity for destruction of digitoxin by the body, for when 0.2 mg. or more digitoxin is given per day (see also previous study[3]), despite the increased amount renally excreted, the amount still left for parenchymal destruction (over 50 micrograms) appears to be too great for the very limited internal processes of destruction, and toxicity results.

These results shed considerable light upon the problem of elimination of digitalis by the digitalized patient. Pardee[5] believed that administered digitalis disappeared from the body *solely by excretion* and he postulated that the maximal rate of elimination was about 0.13 Gm. of digitalis per day. Gold and De Graff[6] on the other hand, concluded that the patient excreted only a *percentage* (possibly fixed) of the total amount of digitalis in the body. Our own observations indicate that the patient excretes a fixed percentage either of the total amount of digitalis in the body or of the daily amount given after adequate digitalization has been obtained. Just as important perhaps is the discovery that a fixed but very small amount also is probably *destroyed* in the body.

The rather fixed fraction of digitoxin excreted by the kidney and the sharply limited ability of the body to destroy no more than half of 100 micrograms of the drug per day explain the ease with which overdosage with this drug can occur. The excretory and neutralizing powers of man thus appear to be narrow and inelastic in respect to the handling of this steroid.

Summary

Patients suffering from acute left ventricular failure, excrete digitoxin as efficiently as normal subjects of the same age period. The addition of right ventricular failure, however, diminished renal excretion of digitoxin markedly but for only 24 hours. Compensated cardiac patients excrete digitoxin at the same rate as the normal subject (30 to 40 per cent of the daily dose). The patient who exhibits toxicity from overdosage with digitoxin, excretes over twice as much digitoxin as the adequately digitalized patient. On the basis of these results, the probable maximal capacity of the body to destroy digitoxin is about 50 micrograms per day.

Acknowledgments

The authors wish to express their thanks to Pamela Angwin, Tadashi Ishida, and Amy Lin for their valuable technical assistance.

REFERENCES

[1] Friedman, M., Bine, R., Jr., and Byers, S. O.: Urinary excretion of digitoxin in the rat. Proc. Soc. Exper. Biol. & Med. **71:** 406, 1949.

[2] St. George, S., Bine, R., Jr., Friedman, M., and Bland, C.: Renal excretion of digitoxin in the rabbit and dog. Proc. Soc. Exper. Biol. & Med. **78:** 504, 1951.

[3] Friedman, M., Bine, R., Jr., Byers, S. O., and Bland, C.: The renal excretion of digitoxin in the normal subject after single and continuous administration of the drug. Circulation **2:** 749, 1950.

[4] St. George, S., Bine, R., Jr., and Friedman, M.: The role of the liver in excretion and destruction of digitoxin. Circulation **6:** 661, 1952.

[5] Pardee, H. E. B.: Notes on digitalis medication. I. The rate of disappearance of digitalis from the body. J. A. M. A. **73:** 1822, 1919.

[6] Gold, H., and De Graff, A. C.: Studies on digitalis in ambulatory cardiac patients. II. The elimination of digitalis in man. J. Clin. Investigation **6:** 613, 1929.

Estrogen-Induced Regression of Coronary Atherosclerosis in Cholesterol-Fed Chicks

By Ruth Pick, M.D., Jeremiah Stamler, M.D., Simon Rodbard, M.D., Ph.D., and Louis N. Katz, M.D.

The present study demonstrates that estrogens reverse previously induced coronary atherosclerosis in cholesterol-fed cockerels, despite the continued presence of the atherogenic stimulus in the diet. Aorta atherogenesis remains unaffected. Hypercholesterolemia is moderately enhanced by estrogen administration; total cholesterol–lipid phosphorus (C/P) ratios are depressed to normal levels, consequent upon estrogen-induced hyperphospholipemia.

In a previous study it was shown that estrogen administration prophylactically inhibits the development of coronary atherosclerosis in cholesterol-fed cockerels.[1] The data of the present experiment demonstrate that estrogenic hormone is also capable of reversing previously induced coronary lesions, despite continued cholesterol feeding.

Methods

Fifty 1 day old Hy-line cockerels were received from a commercial hatchery and reared in a battery brooder. They were fed commercial chick starter mash until they were 7 weeks of age. During the next five weeks, they received mash supplemented with 2 per cent cholesterol plus 5 per cent cottonseed oil (2CO). At the conclusion of this period, 10 of the 50 birds were sacrificed; all 10 were found to have aorta and coronary artery lesions. The remaining 40 cockerels were then divided into four groups (table 1); all continued to receive the experimental 2CO diet. In the first pair of groups (groups 1 and 2), the effect of estrogen* on atherogenesis was assayed during the age period 12 to 15 weeks (5 to 8 weeks of cholesterol feeding). In the second pair of groups, estrogen influence was studied during age 15 to 20 weeks (8 to 13 weeks of cholesterol feeding) (table 1). The chicks of groups 1 and 2 were sacrificed at 15 weeks of age, those of groups 3 and 4 at 20 weeks.

At each sacrifice (12, 15 and 20 weeks of age) plasmas were analyzed for total cholesterol and lipid phosphorus according to the methods of Schoenheimer and Sperry[2] and Man and associates,[3] respectively. Thus the plasmas of estrogen-treated birds were analyzed both before and after administration of estrogen was instituted.

At sacrifice the heart and great vessels were inspected for gross atherosclerotic plaques, and graded grossly from 0 to 4 according to criteria previously described.[4] The hearts were then fixed in 10 per cent formaldehyde. Two blocks were cut from each heart. Two frozen sections were then cut from different levels of each block and stained with Sudan IV for lipids. When no coronary atherosclerotic lesions were found in these four sections, eight further blocks were cut from these hearts and treated similarly. After frozen sections were prepared, the blocks were embedded in paraffin and slides stained with hematoxylin and eosin and with van Gieson's connective tissue stain. Absence of lesions in these 20 sections was the criterion for designating a heart as negative for coronary atherosclerosis. Further, regression of coronary lesions was identified, based upon the presence of fibrosis with little or no associated lipid deposit. An attempt was also made to assess the intensity of atherogenesis in the hearts of birds with lesions. Toward this end a count was made of the number of vessels exhibiting lesions, in relation to the total number of vessels seen in the first two sections from the first two blocks.[5] This count gave an index of the incidence (degree, hence severity) of coronary atherogenesis in a given heart and in the hearts from a given group of birds (table 3).†

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* Estrogen used was estradiol benzoate, 1 mg. daily intramuscularly. We are greatly indebted to Dr. Abbott Allen of the Schering Corp., Bloomfield, N. J. for generous supplies of Progynon B.

† In this initial effort at grading of coronary lesions, the criterion for designating a vessel as positive for atherosclerotic involvement was presence of lipid in any layer of the vessel wall, whether intra- or extracellular, diffuse or focal, associated or unassociated with lipophage accumulation and fibroblast proliferation. This criterion was utilized, although it was

TABLE 1.—*Experimental Regimens after Division into Groups*

Groups	Regimen During 12th–15th Weeks of Age	Regimen During 15th–20th Weeks of Age
1	2CO	—
2	2CO plus estrogen	—
3	2CO	2CO
4	2CO	2CO plus estrogen

TABLE 2.—*Effect of Estrogens on Aorta Atherogenesis in Cholesterol-Fed Chicks*

Group	Age at Sacrifice	Duration of Cholesterol Feeding	Duration of Estrogen Administration	Incidence of Aorta Lesions	Grade of Aorta Lesions
	weeks	*weeks*	*weeks*	%	
Pre-Division	12	5	0	100	2.1
1. 2CO	15	8	0	100	3.5
2. 2CO plus estrogen	15	8	3	100	3.2
3. 2CO	20	13	0	100	4.2
4. 2CO plus estrogen	20	13	5	100	5.0

feeding, aorta atherogenesis became progressively more severe. Estrogen exhibition was completely without effect on this process. The only gross difference was the more vividly yellow color of lesions in the estrogen-treated birds. The microscopic appearance of aorta lesions from chicks of both groups was typical of cholesterol-induced atherosclerosis.

Coronary Arteries. The hearts appeared grossly normal. On microscopic examination all cholesterol-fed control (non estrogen-treated) animals showed a marked degree of coronary atherosclerosis, ranging from single-layer, foam-cell intimal cushions to huge lipid-laden atherosclerotic plaques. A high percentage of vessels was involved in the pathologic process. No signs of spontaneous regression of the lesions was noted in any of the animals.[7] In the estrogen-treated groups a significantly modified picture was encountered. In group 2, treated with estrogens for only three weeks, the lesions tended to be very small, exhibiting only slight fibrosis and containing little or no stainable lipid. When present, this lipid deposition was located chiefly in the outer layers of the media and adventitia, leaving the intima lipid free. Concomitantly, a greater than usual accumulation of fat was frequently present in the perivascular connective tissue in close proximity to the adventitia.

At the 20-week sacrifice, the differences between control (group 3) and experimental (group 4, estrogen-treated for five weeks) were even more marked (table 3). Estrogen-induced regression of coronary lesions was almost com-

TABLE 3.—*Effect of Estrogens on Plasma Lipids and Coronary Atherogenesis in Cholesterol-Fed Chicks*

Group	No. of Birds	Age	Duration of Cholesterol Feeding	Duration of Estrogen Administration	Plasma Total Cholesterol*	Plasma C/P Ratio*	Birds with Coronary Lesions†	Degree of Involvement of Coronary Vessels Count† %‡
		weeks	*weeks*	*weeks*	*mg. %*		%	
3	7	20	13	0	870§ (503–1697)	42.7 (27.8–98.0)	100	119/197 = 60%
4	9	20	13	5	1305 (753–2188)	12.0 (8.5–15.9)	67	2/237 = 0.8%

* Bleeding at sacrifice.

† Cf. text for criterion of freedom from coronary lesions, i.e., absence of lesions in 20 sections from 10 blocks.

‡ Counts were made on two sections taken from the first two blocks; the numerator is the no. of vessels with lesions (including lipid infiltration, atheroma, atherosclerotic plaque—see text), the denominator is the total no. of vessels seen; both numerator and denominator are the sum for the particular group.

§ Values enclosed in parentheses are the ranges which determined the mean values.

RESULTS

1. *Pathologic Findings*

Aorta. Gross aorta findings are summarized in table 2. With prolongation of cholesterol

recognized that mere presence of lipid, per se, in the vessel wall is not adequate to justify a pathologic diagnosis of atherosclerosis. Atherosclerosis, by definition, is a thickening of the arterial wall, resulting from a complex tissue reaction, of which lipid accumulation is only one component.[6] In subsequent applications of this grading method, the vessels visualized were divided into three catagories: normal, positive for lipid infiltration only, positive for atherosclerosis.

plete. Three birds were entirely free of lesions. Multiple sections of hearts of six other chicks revealed an occasional vessel which exhibited a residual plaque. These few remaining lesions were similar morphologically to those observed in the estrogen-treated birds at the 15-week sacrifice. Altogether, only four plaques were seen that exhibited the appearance of a well developed lesion without signs of regression. In the lesions that showed regression, van Gieson's connective tissue stain revealed only a few strands of very fine young fibrous tissue.

2. *Biochemical Findings*

The mean value for total plasma cholesterol was similar in the control and the experimental groups before estrogen treatment was instituted (for example, in groups 3 and 4 at 15 weeks of age, a value of 1012 and 1015 mg. per 100 ml., respectively). After estrogen therapy the plasma total cholesterol in the treated group was moderately higher (table 3). The most significant change occurred in the lipid phosphorus levels. These rose, consequent upon estrogen-induced hyperphospholipemia, from an average of 17.9 mg. per 100 ml. before treatment to 108.7 mg. per 100 ml. after five weeks on estrogen. Therefore, the total cholesterol–lipid phosphorus (C/P) ratio fell from an average of 56.7 to 12.0 (table 3).

Discussion

The foregoing findings demonstrate that estrogen effects regression of cholesterol-induced coronary atherosclerotic lesions in chicks, despite continued presence in the diet of the atherogenic stimulus. Thus, estrogen is effective against *coronary* atherogenesis in both prophylactic and therapeutic-type experiments. In accordance with our observations in the former study,[1] estrogen was again completely without influence on *aorta* atherogenesis.

The results of this experiment confirm the thesis that atherosclerosis is a reversible process.[8] Moreover, they represent a significant extension of our information concerning regression (healing, reversibility) of experimental atherosclerosis. Previous studies of regression involved the effects, principally on the aorta, of cessation of cholesterol feeding.[9-11] Definite regression of the pathologic process is demonstrable under this circumstance. The present study further shows that: (1) regression may be effected during continued ingestion of cholesterol; (2) this estrogen-induced regression may be remarkably effective; (3) it may involve clearing of both lipidosis and fibrosis from the vessel wall; (4) it may have a high preferential selectivity for the coronary arteries.

The mechanism of estrogen-induced regression of coronary lesions remains obscure. Several possibilities suggest themselves: Conceivably—from the peculiar histologic picture of the lesions showing partial regression—estrogen may induce lipophage activity which effects movement of lipids towards the adventitia and the perivascular tissue. Likewise, estrogen may decrease permeability of the endothelium for lipids. In addition to these possible actions of estrogen on vascular tissue, the effects of the hormone on plasma lipid-lipoprotein complexes may be key factors altering atherogenesis. These possible mechanisms, obviously hypothetic at the present stage of knowledge, hardly seem to account for one significant phenomenon observed in these experiments: regression of coronary lesions without effect on aorta atherogenesis. This finding may be related to metabolic differences (qualitative and/or quantitative) between vascular tissue of the aorta and the heart. Further work is necessary to clarify these new problems posed by our data.

Summary

1. Estrogen reverses coronary atherosclerosis in cockerels previously induced by cholesterol feeding, despite continued feeding of the cholesterol diet.

2. This estrogen-induced regression occurs in the presence of continued marked hypercholesterolemia, of reversal of previously elevated total cholesterol–lipid phosphorus (C/P) ratios to normal levels, and of persistent aorta atherogenesis.

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REFERENCES

[1] Pick, R., Stamler, J., Rodbard, S., and Katz, L. N.: Inhibition of coronary atherosclerosis by estrogens in cholesterol-fed chicks. Circulation **6:** 276, 1952.

[2] Schoenheimer, R., and Sperry, W. M.: A micromethod for the determination of free and combined cholesterol. J. Biol. Chem. **106:** 745, 1934.

[3] Man, E. B., and Peters, J. P.: Gravimetric determination of serum cholesterol adapted to the Man and Gildea fatty acid method, with a note on the estimation of lipid phosphorus. J. Biol. Chem. **101:** 685, 1933.

[4] Horlick, L., and Katz, L. N.: The relation of atheromatous development in the chicken to the amount of cholesterol added to the diet. Am. Heart J. **38:** 336, 1949.

[5] Paterson, J. C., and Mitchell, C. A.: Experimental coronary sclerosis. IV. The effect of cortisone on end-stage coronary sclerosis in chickens. Arch. Path. **52:** 260, 1951.

[6] Katz, L. N., and Stamler, J.: Experimental Atherosclerosis. Springfield, Ill., Charles C Thomas. (In press.)

[7] Rodbard, S., Pick, R., Bolene-Williams, C., and Katz, L. N.: Age-conditioned spontaneous regression of atherosclerosis in the cholesterol-fed chick. Circulation **6:** 459, 1952.

[8] Wilens, S. L.: The resorption of arterial atheromatous deposits in wasting disease. Am. J. Path. **23:** 793, 1947.

[9] Horlick, L., and Katz, L. N.: Retrogression of atherosclerotic lesions on cessation of cholesterol feeding in the chick. J. Lab. & Clin. Med. **34:** 1427, 1949.

[10] Anitschkow, N.: Ueber die Rueckbildungsvorgänge bei der experimentellen Atherosclerosis. Verhandl. deutsch. path. Ges. **23:** 473, 1928.

[11] Bevans, M., Davidson, J. D., and Kendall, F. E.: Regression of lesions in canine arteriosclerosis. Arch. Path. **51:** 228, 1951.

Skin Temperature Response of Normal Human Subjects to Various Conditions

By WALTER REDISCH, M.D., EDWARD SHECKMAN, M.D., AND J. MURRAY STEELE, M.D.

Ten healthy volunteers (five males and five females), 25 to 41 years of age, were exposed to several different environmental conditions in a constant temperature room. It was found that at 20 C. and about 55 per cent humidity, about five hours after the last meal, the behavior of the temperature of the toe in contrast to that of the finger was consistent, reliable and reproducible. These conditions, somewhat cooler than those frequently used, were deemed suitable for testing vasodilator drugs or procedures.

INVESTIGATION of skin temperature has generally been conducted at environmental temperatures between 23 C. and 31 C. This range represents the approximate limits of the zone of vasomotor regulation or the condition of comfort.[1-3] The environmental conditions most often selected have been temperatures from 24 to 27 C., relative humidity of 40 to 50 per cent, and wind velocity of less than 1 meter per second. The subject was generally in the basal state, awake, lightly clothed, and in a semireclining or supine position. Most of the work in this field has been carried out within these limits.[1-5]

These conditions, however, were found to be unsuitable for testing the effect of vasodilator drugs on skin temperatures, for two reasons: first, the period of time necessary for adaptation was impracticably long and spontaneous variations in temperatures recorded interfered with the interpretation of the curves; second, it was necessary to have the room cool enough to maintain the extremities in gentle vasoconstriction so that dilation of the vessels could be readily recognized.

It has been shown that even under carefully controlled conditions within the zone of vasomotor regulation, a period of from one to two hours is required for adaptation to change in environmental temperature, change in posture, and partial disrobing.[6-9] Instability of finger temperatures has been specifically pointed out under various conditions[6, 10, 11, 12] and is apparent, although not specifically mentioned, in curves published by Sheard and his group.[7, 13, 14]

It was the object of this study to learn the most comfortable environmental conditions under which surface temperature of the extremities of normal individuals is sufficiently predictable, reproducible, and cool enough to test vasodilation.

METHODS AND MATERIAL

Experiments were conducted in a constant temperature room. After preliminary trial at various temperatures, two sets of environmental conditions were chosen for further study: 20 C. ± 1 C. and 22 C. ± 1 C., with relative humidity between 51 and 57 per cent and wind velocity at a little less than 1 meter per second. These environmental conditions were each varied further by allowing the patients to have lunch 30 to 90 minutes before beginning the experiment in one series and omitting lunch in another so that the experiment was begun about five hours after breakfast. Ten subjects were tested under all of these four conditions. Five of the subjects were also tested at the lower temperature (20 C.), having fasted since the evening of the previous day except for water. The subjects were healthy adults, five men and five women, varying from 25 to 41 years of age.

The experimental period was 180 minutes or longer, beginning between 12:00 noon and 1:30 p.m. in the first four conditions, and between 9:00 and 10:00 a.m. in the fifth condition. The subjects were supine, head elevated on one pillow, wore cotton pajamas, and were covered with one sheet. They were kept awake throughout the period by means

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of conversation, reading or music. None of the subjects had taken any drug or alcoholic beverage on the day of the experiment or smoked for at least 30 minutes prior to the beginning of the experimental period.

Temperatures were recorded automatically by means of a six point Leeds and Northrup Speedomax. This machine affords an accuracy of ±0.15 C. The rate of recording was such that the temperature at each of the six points was recorded every 22.5 seconds through a three hour experimental period. Thus a quasicontinuous curve was obtained. Welded iron-constantan thermocouples were made from 30 gauge thermocouple wire insulated with extruded nylon. The thermocouples were placed on the skin under a 1 cm. square of foam rubber held in place by scotch tape. The rectal thermocouple was fixed by 00 silk and collodium within a 16 F soft urethral catheter. Temperatures were recorded in all subjects from the midforehead, palmar surface of the terminal phalanx of the right middle finger, and the plantar surface of the distal phalanx of both great toes. Rectal temperatures were recorded in about half the experiments. The sixth thermocouple was used as an exploratory one, temperatures being taken from different sites such as the skin over the zygoma, the xiphoid and the lateral aspect of the leg or thigh.

Results

The five sets of circumstances under which skin temperatures were studied were, then:

1. L–22 C., 30 to 90 minutes after lunch at 22 C.
2. NL–22 C., five hours after breakfast; no lunch; at 22 C.
3. L–20 C., 30 to 90 minutes after lunch at 20 C.
4. NL–20 C., five hours after breakfast; no lunch; at 20 C.
5. NB–20 C., following fast from the previous evening (no breakfast), except for water, beginning at 9 a.m. the next morning.

At the end of the period of study the skin temperatures all were between 18 and 38 C. For purposes of easy description of behavior of skin temperatures, this 20 degree range was divided in four 5 degree zones and the number of individuals falling into each zone counted (table 1).

Table 1.—*Tabulation of 10 Individuals According to Surface Temperatures of Their Extremities at the End of Experimental Period under Four Different Environmental Conditions*

Zones of Temperature	Environmental Conditions*			
	L-22 C.	NL-22 C.	L-20 C.	NL-20 C.
		Toes		
33.1–38 C.	●●			
28.1–33 C.	●●●●	●	●	
23.1–28 C.	●●●	●●	●●●	
18 –23 C.	●	●●●●●●●	●●●●●●	●●●●●●●●●●
		Fingers		
33.1–38 C.	●●●●●●●●●	●●●●●●	●●●●	●●
28.1–33 C.	●	●●●	●●●●	●●●
23.1–28 C.		●	●●	●●●
18 –23 C.				●●

* L—with lunch; NL—without lunch.

Table 2.—*Data on Adaptation of Toes under Five Environmental Conditions*

Adaptation to the various conditions is considered complete for the purposes of this study when the temperature has remained constant within a range of ±1 C. for a period of 30 minutes.

Environmental Condition*	Number Tested	Number Adapted	Average Adaptation Time	Range of Adaptation Temperature
			minutes	*C.*
L—22 C.	10	4	99	25.7–26.5
NL—22 C.	10	9	91	23.2–24.2
L—20 C.	10	7	92	21.7–22.7
NL—20 C.	10	10	60	20.5–21.5
NB—20 C.	5	5	118	20.5–21.5

* L—with lunch; NL—without lunch; NB—without breakfast.

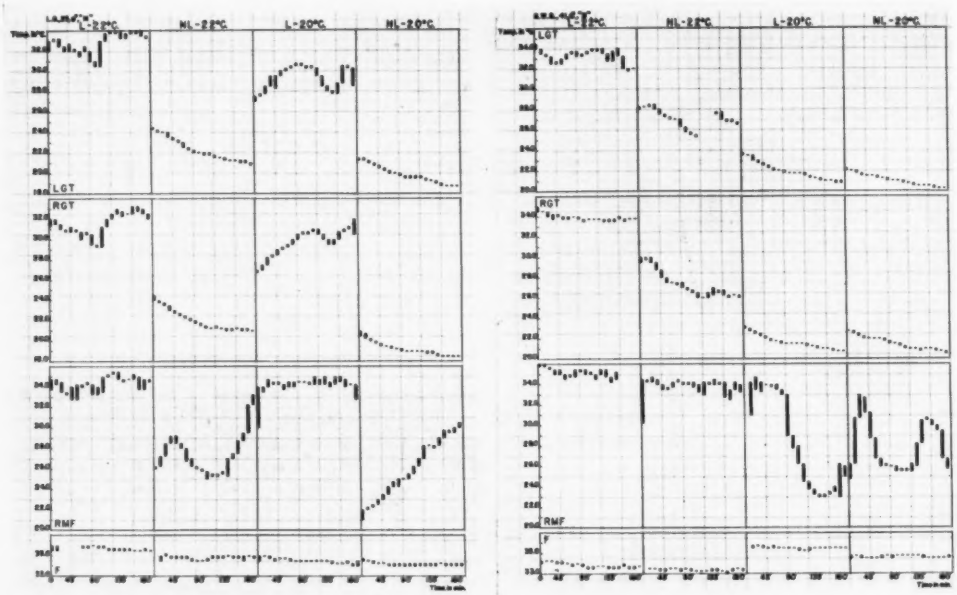
Toes: As the conditions are changed successively from condition 1 to condition 5, the frequency with which toe temperatures reach the

lower zones increases progressively (table 1). In L–22 C. the distribution is more widely spread and there is little tendency for the toe temperatures to fall. Under conditions NL–20 C. and NB–20 C., only once did a toe fail to reach the lowest temperature zone. Under conditions NL–22 C. and L–20 C. the pattern of distribution is intermediate between these two extremes with the majority of toes ending in zone 18 C. to 23 C.

Fingers. The number of individuals whose finger temperatures remained in zone 23 C. to 28 C. also become progressively fewer as conditions are changed in succession from L–22 C. to NB–20 C. Very few finger temperatures fall into zone 18 C. to 23 C., however, either at the beginning or at the end of the experimental periods (table 1).

In general, the temperature of the toes begins at a lower level than that of the fingers, shows a much more consistent and marked tendency to fall, and ends at a much lower level than that of the fingers. These differences are least apparent in condition L–22 C. and most apparent in NL–20 C. and NB–20 C. (table 2).

Forehead. The temperatures taken from the forehead began and remained in the highest zone throughout all but two of the 45 experiments. In those two exceptions, both under condition 5, the temperatures were between 32 C. and 33 C.



FIGS. 1 (*left*) and 2 (*right*). Simplification of quasicontinuous curves of temperatures taken from the great toes, finger, and forehead, under conditions 1 to 4 for each individual. The columns represent the range of the temperatures taken at the designated point in each of the 20 successive nine-minute periods.

LGT—left great toe; RGT—right great toe; RMF—right middle finger; F—forehead; Ordinate—temperatures in degrees centigrade; Abscisse—time in minutes.

The time taken for the temperature of the *toes* to arrive at a sufficiently steady state to test for a vasodilator effect was usually about 90 minutes, although usually a steady downward trend would permit testing within 45 minutes to an hour (figs. 1, 2, and 3). On the other hand, the *fingers* usually failed to behave in a predictable fashion. Even under the coolest environmental and strictest basal conditions imposed, they continued, as has often

been reported, to fluctuate widely and irregularly. The fingers are, therefore, obviously not suitable for testing vasomotor drugs.

With the exception of three instances occurring in different individuals, the temperature of the *forehead* was stable and adapted from the onset of the experiments.

range in all individuals under all conditions and showed no tendency to change throughout the experimental periods. The temperatures over the *zygoma*, over the *xiphoid process* of the sternum and the lateral aspect of the *leg* and *thigh* behaved similarly to the forehead temperatures but at lower levels. Temperatures

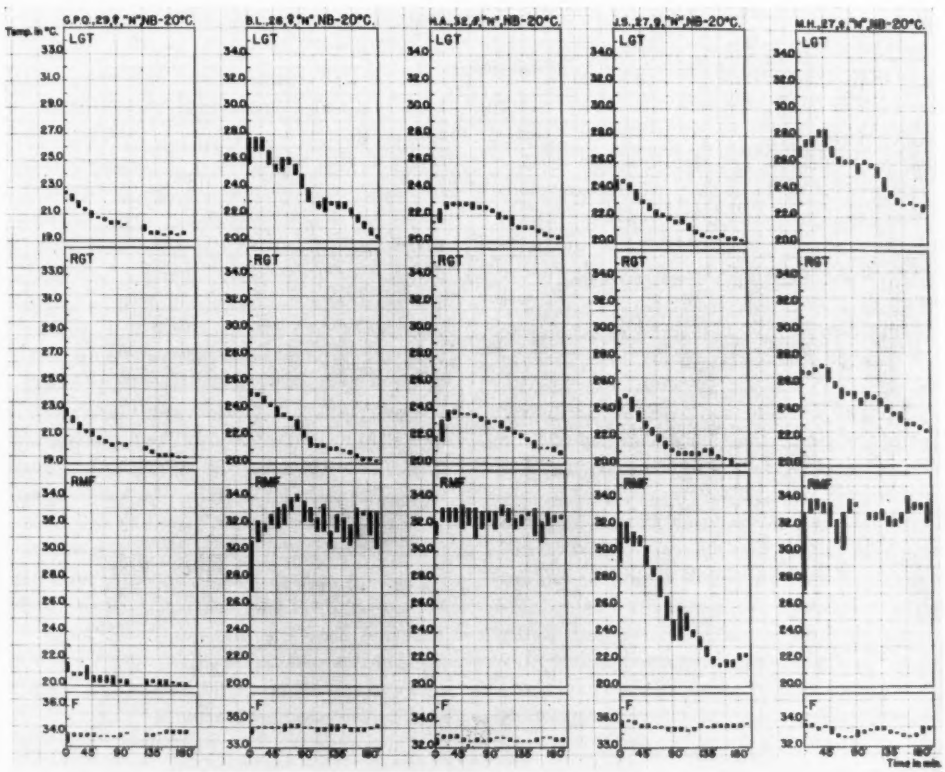


FIG. 3. Simplification of quasicontinuous curves of temperatures taken from the great toe, finger and forehead for the five individuals tested under condition 5. The columns represent the range of the temperatures taken at the designated point in each of the 20 successive nine-minute periods.

LGT—left great toe; RGT—right great toe; RMF—right middle finger; F—forehead; Ordinate—temperatures in degrees centigrade; Abscisse—time in minutes.

The height of the column in the abstracts of the temperature records (figs. 1, 2, and 3) affords an index of the spontaneous variations during any given period of time. The variability of the surface temperature of the finger, regardless of the environmental conditions or metabolic state, in contradistinction to that of the toes, is readily apparent.

The *rectal temperatures* were within normal

taken over the zygoma fell within the range of 32.2 C. to 36.5 C.; those taken over the lateral aspect of the leg ranged between 29.2 C. and 35 C., while temperatures over the xiphoid ranged from 32.7 C. to 37 C.

DISCUSSION

A test of vasodilator activity is necessarily based on release from a state of vasoconstric-

tion. To compare various substances accurately, the stimulus to constriction should be uniform. In this study, a standard period of inactivity in a comfortable, cool environment, and, in more than half of the experiments, the withholding of food, have been the stimuli used to produce, in a relatively short time, a standard state of increased vasomotor tone in normal individuals.

The variability of finger temperature is consistent with the concept that the fingers participate to a greater extent than any other area in the fine adjustments of the heat dissipation mechanism. The temperature of the finger becomes more stable at high environmental temperatures, when it approaches "maximal vasodilation."[15] At such temperature levels response to vasodilating agents or procedures cannot be expected. The fingers might more readily be employed to test vasoconstrictor drugs. If environmental temperatures are low enough to cool the fingers, temperatures considerably below the lower temperature used in this study would be necessary and would involve considerable discomfort for the subject.[4]

The forehead temperatures as well as those of the face, trunk, and the upper portions of the extremities show great stability. Consequently, relatively small changes in the temperature of these areas after the use of an agent or procedure can be regarded as significant. Insofar as the forehead is concerned, a relatively abrupt rise of temperature of as little as 1 degree cannot be expected to occur spontaneously.

The patterns of response in the toes differed greatly under the five conditions. Under condition L–22 C. adaptation occurred in less than half of the individuals and when it did occur, was late and at relatively high temperature. In at least half of the subjects, curves were generally unstable. Consequently, this condition must be regarded as unsuitable for experiments with vasodilating agents or procedures.

Under condition NL–20 C. temperature of the toes reached a steady enough state at suitable levels quickly enough to be practical for study of vasodilator drugs. A variation away from the trend of two degrees or more, after an adaptation period of an hour would be unlikely to occur by chance.

Under condition NB–20 C. (fig. 3) adaptation or the establishment of a reliable trend occurred in all cases, but later than under any of the other conditions. This condition was not considered practical because the subjects were restless and complained of cold, hunger and drowsiness.

Some individuals adapt well without lunch at 22 C. and others adapt well at 20 C. with lunch (figs. 1 and 2). All subjects, however, adapted well when the lower temperature and fasting were both imposed. It is concluded that condition NL–20 C. is the most suitable for experiments designed to test and compare vasodilating agents or procedures by means of skin surface temperature of the lower extremities, specifically the plantar surface of the toes.

Striking qualitative differences in the patterns of response of the terminal phalanges of the extremities and other areas of skin to various stimuli are apparent. The forehead, trunk, thigh and leg remain close to body temperature. The terminal phalanges vary so widely that it is evident that they are the principal participants in the mechanisms responsible for regulation of heat loss. The coarse adjustment appears to be chiefly accomplished by the toes. The fact that the fine minute to minute adjustment is accomplished by the fingers may easily account for their unreliability as a test object for vasodilator effects.

Summary

1. A study of several environmental conditions has shown that at 20 C. with a humidity of 50 to 55 per cent after a fast of at least four hours, the temperature of the skin of the plantar surface of the toes of most normal individuals is a suitable test object for vasodilator effects. Under these circumstances a steady downward trend or stabilization of surface temperature will usually take place within an hour. A rise of 2 degrees or more can, therefore, be attributed to the effect of a vasodilator agent since it would not be expected to occur spontaneously.

2. The temperature of the skin of the fingers

is too variable to be suitable for testing vasodilator agents under any of the conditions tested.

3. The forehead, trunk, thigh and leg are characterized by stable temperature curves at levels near rectal temperature. These sites are considered suitable for the testing of vasodilating agents and procedures insofar as they affect the "blush" areas. A rise of 1 C. or more in these areas cannot be expected to occur spontaneously.

REFERENCES

[1] WINSLOW, E. A., HERRINGTON, L. P., AND GAGGE, A. P.: Physiological reactions of the human body to varying environmental temperatures. Am. J. Physiol. **120:** 1, 1937.

[2] GAGGE, A. P., WINSLOW, E. A., AND HERRINGTON, L. P.: Influence of clothing on physical reactions of the human body to varying environmental temperatures. Am. J. Physiol. **124:** 30, 1938.

[3] MCCONNELL, W. J., AND YAGLOGLOU, C. P.: Correlation of skin temperatures and physiological reactions. Tr. Am. Soc. Heat. & Vent. Eng. **30:** 305, 1924.

[4] HOUGHTON, F. C., AND YAGLOGLOU, C. P.: Determining lines of equal comfort. Tr. Am. Soc. Heat. & Vent. Eng. **29:** 163, 1923.

[5] WINSLOW, E. A., HERRINGTON, L. P., AND GAGGE, A. P.: Physiological reactions of the human body to various atmospheric humidities. Am. J. Physiol. **120:** 288, 1937.

[6] COBET, R., AND BRAMIGK, F.: Ueber Messung der Waermestrahlung der menschlichen Haut. Arch. klin. Med. **144:** 45, 1934.

[7] ROTH, G. M., WILLIAMS, M. M. D., AND SHEARD, C.: Changes in skin temperature of the extremities produced by changes in posture. Am. J. Physiol. **124:** 161, 1938.

[8] FREEMAN, H., AND NICKERSON, R. F.: Skin temperature of normal individuals under cold conditions. J. Nutrition **15:** 597, 1938.

[9] NIELSON, M., HERRINGTON, L. P., AND WINSLOW, E. A.: Effect of posture on peripheral circulation. Am. J. Physiol. **127:** 573, 1939.

[10] KUNKEL, A. J.: Ueber die Temperatur der menschlichen Haut. Ztschr. Biol. **25:** 55, 1889.

[11] BURTON, A. C., AND TAYLOR, R. M.: A study of the adjustment of peripheral vascular tone to the requirements of the regulation of body temperature. Am. J. Physiol. **129:** 565, 1940.

[12] STEELE, J. M.: Fever in heart failure. Relations between the temperatures of the interior and the surface of the body. J. Clin. Investigation **13:** 869, 1934.

[13] SHEARD, C.: Temperatures of the skin and thermal regulation of the body. In Otto Glasser: Medical Physics. Chicago, Yearbook Publishers, 1944. P. 1523.

[14] WILLIAMS, M. M. D., HORTON, B. T., AND SHEARD, C.: The relationship between skin temperature of the extremities and the effective temperature scale. Proc. Staff Meet., Mayo Clin. **14:** 668, 1939.

[15] FETCHER, E. S., HALL, J. F., JR., AND SHAUB, H. G.: The skin temperature of an extremity as a measure of its blood flow. Science **110:** 422, 1949.

Mitral Stenosis with Exertional Cyanosis and Pulmonary Hemosiderosis

By JAMES A. WIER, M.D., AMO J. PICCOLI, M.D., DAVID G. GREENE M.D., AND CLAYTON W. GREENE, M.D.

A patient with mitral stenosis is reported who suffered from exertional cyanosis for the last eight years of his life. Radiologic examination of his chest demonstrated a diffuse pulmonary hemosiderosis, which was confirmed at autopsy. Physiologic studies in the last few weeks of life showed that the cyanosis was not due to impairment of oxygenation of the blood in the lungs but rather to slowed circulation, possibly augmented by local changes in the anatomy of the vessels of the skin.

THE OCCURRENCE of cyanosis in patients with mitral stenosis has long been noted, and cyanosis of the lips, ears and cheeks, the "mitral facies," has been considered typical of that lesion. The subject has been reviewed by Cossio and Berkonsky,[1] who reported clinical and physiologic studies in 20 cases of mitral stenosis with cyanosis. In six of these patients they attributed the cyanosis to stasis of the circulation, as indicated by a high arteriovenous difference in the oxygen content of blood in peripheral arteries and veins. In 10 other patients they found both stasis and arterial oxygen unsaturation. In the remaining four patients the data did not explain the cyanosis but the authors postulated the presence of dilated venous capillaries in the skin. In no patient was arterial oxygen unsaturation the only cause of the cyanosis.

Conspicuous granular hemosiderosis of the lungs, an uncommon complication of mitral stenosis, is usually discovered radiographically and is sometimes confused with other causes of miliary densities or calcification in the lungs. Pendergrass, Lame and Ostrum[2] were able to find only 17 cases with autopsy. Reports based on radiographic studies alone would increase this total.[3, 4, 5] No report of pulmonary function or arterial oxygen saturation studies in such cases has been found. Cyanosis has not been mentioned prominently in the case histories.

This report presents a case of mitral stenosis with severe exertional cyanosis. Despite the roentgenographic and pathologic findings of extensive pulmonary hemosiderosis, physiologic appraisal of cardiac and pulmonary function indicate that the cyanosis was chiefly a stasis phenomenon, rather than secondary to the anatomic changes in the lungs.

CASE REPORT

Clinical Data

E. B., a 46 year old white accountant, first consulted one of us (C. W. G.) because of increasing dyspnea on exertion of three months duration. His past history included recurrent attacks of rheumatic fever between the ages of 12 and 15 years with sufficient recovery to play semiprofessional baseball without difficulty. Cyanosis on exertion had been present for eight years, and for several years he had limited his activity because of shortness of breath and fatigue. These were not bothersome complaints until about three months before he was first seen. He complained also of increasing fatigue, insomnia and slight ankle edema, of recent development.

He was strikingly cyanotic after the slightest exertion, but after a few minutes rest in a warm room his color returned to normal. The cyanosis involved lips, nail beds, ears, cheek and trunk particularly. The other important physical findings included a totally irregular heart with a loud, blowing apical systolic murmur, accompanied by a split first sound. The second sound in the pulmonary area was accentuated. A diastolic murmur at the apex was audible distinctly at times, but at other times no diastolic murmur could be heard. The liver was enlarged 8 cm. below the costal margin but was not tender. There was slight ankle edema. The lungs were normal on physical examination. Routine laboratory findings were not remarkable except for a

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terminal urinalysis which showed albumin and microscopic red and white blood cells, and the electrocardiogram which showed auricular fibrillation and right ventricular preponderance.

X-ray examination revealed the cardiac shadow to be considerably enlarged (fig. 1). The left auricle, pulmonary artery and right ventricle were enlarged, and the vascular markings were increased in the hilar areas bilaterally. In addition, the lung fields showed diffuse, small, evenly distributed nodulations (fig. 2), and a few irregular pea-sized areas of calcification scattered over the lower lung fields. It was felt that the cardiac silhouette was quite typical of mitral stenosis and that the pulmonary changes were those of nodular hemosiderosis.

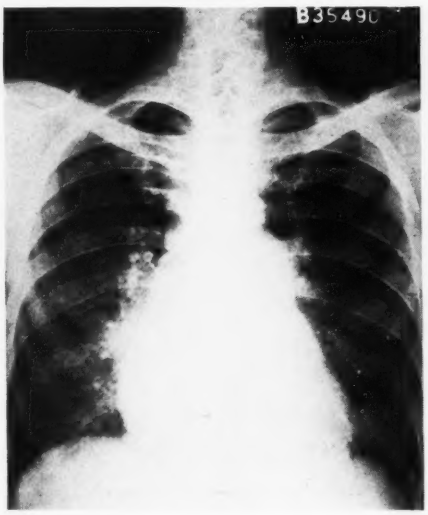

FIG. 1. Posterior-anterior roentgenogram of the chest.

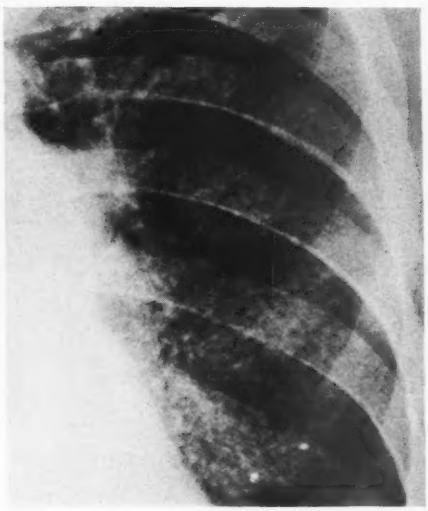

FIG. 2. Detail of the chest roentgenogram.

Under observation his dyspnea and fatigability progressed rapidly although, disregarding advice, he continued to work for five months. Two weeks before he died he was persuaded to enter the hospital briefly for diagnostic studies, including cardiac catheterization. He remained thereafter at rest at home until 24 hours before death when he was readmitted because of increasing dyspnea and ankle edema, insomnia and fatigability. His lungs remained clear on auscultation until the time of death.

Physiologic Data

During the last month of his life this patient's cardiopulmonary function was studied using the procedures of Baldwin, Cournand and Richards[6] and by cardiac catheterization. Blood pressures were recorded by a Hathaway blood pressure recording system.[7] The results appear in table 1. Vital capacity and maximal breathing capacity were reduced to 70 and 55 per cent of normal, respectively. Hyperventilation was present at rest and was prolonged during the period of recovery after the standard exercise to such an extent that ventilation was still increasing at the end of the fourth minute. The oxygen consumption was normal at rest but failed to increase normally during the standard exercise. The rate of oxygen removal from each liter of ventilation was low at rest and fell even lower during exercise. The arterial oxygen saturation was slightly below normal at rest and after exercise rose to normal. The pulse rate rose so that an accurate count was not obtained but was still 160 at the sixth minute of recovery. Dyspnea persisted for 10 minutes. The pressures in the pulmonary artery and the right ventricle revealed hypertension of the pulmonary vascular system and also an elevated diastolic pressure in the right ventricle, indicative of right heart failure. The arteriovenous difference in blood oxygen content was increased to more than twice the normal value. Cardiac output and stroke volume were greatly reduced.

Pathology

Post-mortem examination was performed five hours after death. (Buffalo General Hospital autopsy number 7082.)

The noteworthy findings included marked cyanosis about the face, neck and upper chest, ears, lips and fingernails. Each pleural cavity contained 150 cc. of clear straw-colored fluid. The lungs appeared fairly well expanded and had the characteristic color and consistency of "brown induration"

TABLE 1.—*Results of Function Studies*

	Observed	Predicted[6]
I. Pulmonary function tests, one month before death		
Vital capacity, cc.	2850	4100
Maximal breathing capacity, L./min.	63	115
Ventilation, L./min./M.² body surface		
Rest	5.1	3.1
Exercise	11.5	10.0
1st minute of recovery	11.1	13.4
2nd minute of recovery	12.0	9.4
4th minute of recovery	14.7	—
Pulse rate		
Rest	86	—
6th minute of recovery	160	—
Oxygen consumption		
cc./min./M.² body surface		
Rest	134	131
Exercise	257	481
cc./L. of ventilation		
Rest	29.6	46.1
Exercise	25.0	55.7
Arterial blood	Rest	Recovery
Oxygen content, vols. %	20.0	20.9
Oxygen capacity, vols. %	22.0	21.9
Oxyhemoglobin saturation, %	91.7	96.3
Carbon dioxide tension, mm. Hg	31	23
II. Cardiac catheterization, two weeks before death. (Representative values taken from a series of observations on one day.)		
Blood pressures, mm. Hg		
Femoral artery	96/65	
Right ventricle	84/10	
Pulmonary artery	82/51	
Peripheral venous pressure, mm. saline	165	
Arteriovenous oxygen difference, vols. % (simultaneous pulmonary and femoral arterial samples)	12.0	
Cardiac output, L./min.	1.76	
Cardiac index, L./min./M.² body surface	0.97	
Stroke volume, cc.	22	

seen in chronic passive congestion. On various sections a state of congestion was obvious, but edema was minimal. Palpation of the lower portions of the lungs disclosed numerous grayish-white bony pellets, varying in size from that of a pinhead to that of a small pea.

The pericardial surface was smooth and glistening, and the pericardial cavity contained 50 cc. of clear, straw-colored fluid. There was distinct enlargement of the heart, particularly of the right side. The heart weighed 560 Gm. The right ventricle and right atrium were both distended. The enlarged tricuspid valve measured 16.3 cm. in circumference; the pulmonary valve measured 10 cm. In structure these valves were otherwise normal. The pulmonary artery was dilated and showed arteriosclerosis ex-

FIG. 3. Postmortem roentgenogram of the right lung.

tending out into the major branches. There was marked dilatation of the left atrium which contained a large mural thrombus firmly attached to the wall. The auricular appendage also contained thrombi. The mitral ostium was severely stenosed and had a typical fishmouth appearance. Both cusps were firm and indistinguishably fused to each other with their edges diffusely thickened and fibrotic. No vegetations were present. The circumference of the mitral ring was 4.1 cm. The aortic valve measured 6.6 cm. in circumference and revealed a slight degree of calcific stenosis. The left and the posterior semilunar leaflets were adherent to each other. The average thickness of the right ventricle measured at the pulmonary conus was 0.6 cm, and that of the left measured at the anterior wall was 1.5 cm. There

was moderate arteriosclerosis of the coronary arteries with little or no narrowing of their lumina.

The abdominal cavity contained 1500 cc. of ascitic fluid. The liver weighed 1300 Gm. It was firm and on section showed the nutmeg appearance of chronic passive congestion. The spleen was enlarged, firm, weighed 340 Gm. and appeared congested. At the root of the mesentery at an area supplying the midportion of the ileum a partially calcified tuberculous node was found, but there were no mucosal scars. Postmortem roentgen photogram of the right lung shows very clearly the uniform finely granular, whitish shadows as well as a few small calcified nodular osteomas (fig. 3). The photogram of the left lung is of identical appearance.

Upon microscopic examination the most impressive features were the nodular focal deposits of granular hemosiderin which were found in abnormal amounts scattered throughout the lungs, both intra-alveolar and interstitial in position (fig. 4). These hemosiderin deposits were predominantly intra-alveolar, however, expanding the alveolar walls and moderately compressing the surrounding alveoli. Many subpleural deposits of hemosiderin were noted. In addition, there was a diffuse spread of hemosiderin-laden cells in groups of two or three throughout the lung. In specific stains for iron pigment (Prussian blue) these focal deposits were strongly positive. A bluish imbibition of the stroma about the hemosiderotic areas was noted.

Cuboidal endothelium (occasionally referred to as alveolar epithelium) was noted lining many alveoli (fig. 5). It was similar to that frequently found associated with partial atelectasis or chronic pneumonitis. The interstitial tissue was fairly prominent and in areas showed hyaline degeneration, the septa of the hemosiderin-laden alveoli being especially involved. A small amount of calcification was occasionally noted in the septal fibers and even in the walls of the dilated veins. The characteristic dilatation and tortuosity of chronic passive congestion were seen in the alveolar capillaries. Thrombi were found in some capillaries and in a few small caliber branches of the pulmonary artery. There were no infarct-like hemorrhages. Interstitial hemorrhages surrounding small pulmonary veins were occasionally seen, however.

The liver showed central necrosis, old and recent, and chronic congestive changes. There was marked congestion of the spleen with fibrosis. Distinct edema and diffuse scarring of the myocardium were noted.

FIG. 4. Photomicrogram of the lung showing hemosiderin deposits.

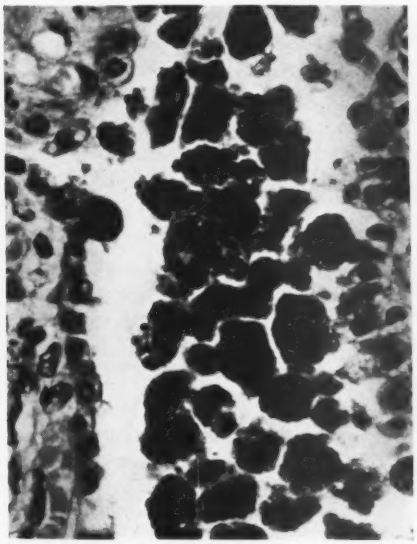

FIG. 5. Photomicrogram of the lung showing cuboidal epithelium lining alveoli.

DISCUSSION

The minimal arterial oxygen unsaturation at rest and the normal arterial oxygen saturation after exercise indicate that failure of oxygenation of blood in the lungs plays essentially no part in the development of this patient's cyanosis. The slow blood flow, on the other hand, is perfectly adequate to account for cyanosis which might have been expected even at rest. Hickam and Cargill[8] have studied the response to exercise of failing hearts whose output could not be increased. They found that a disproportionate increase of the arteriovenous differ-

ence in blood oxygen content is typical. Although this subject's cardiac output was not measured during exercise, it almost certainly would not increase in proportion to the demand for blood flow. With the increased tissue demands for oxygen his arteriovenous oxygen difference increases. The mean capillary oxygen saturation thus falls, and the increased amount of reduced hemoglobin in the capillaries accounts for his cyanosis.

If the cyanosis is due to a limitation of blood flow, it does not seem likely that this limitation of flow has been on the basis of myocardial insufficiency for the eight years preceding death. Had myocardial failure been present all that time, one might have anticipated more of the other signs of myocardial failure and a more rapid progression. An alternative explanation is that an adequate increase of blood flow during exercise was prevented by the extremely small mitral orifice. At the time of the function studies, congestive failure, of course, was present.

One further point in relation to the cyanosis needs emphasis. Lundsgaard and Van Slyke[9] found that particularly in the presence of venous stasis the number, length and width of superficial blood-filled capillaries increased and contributed to the cyanosis. In the present patient in the areas of most pronounced cyanosis over the malar regions and over the ears, small distended venules were apparent on close observation and may have contributed to the cyanosis.

Although the radiologic and pathologic picture of hemosiderosis is a striking one in this patient it apparently had a relatively minor adverse effect on pulmonary function. The arterial oxygen saturation was only slightly reduced at rest, so that the patient was apparently able to compensate for the unfavorable factors revealed by the microscope. This was done only by great hyperventilation and the compensation was not complete. In the face of such severe cardiac dysfunction with pulmonary congestion it is difficult to assay the degree of purely pulmonary disability, and abnormal findings must be interpreted with caution. Many of the abnormalities in this patient point to pulmonary congestion. The spirogram shows slowing of inspiration and expiration of about equal degree, as is seen in patients with diminished pulmonary elasticity. The limitation of vital capacity and maximal breathing capacity are of a moderate degree quite consistent with pulmonary congestion present. The low oxygen consumption during the minute of exercise, not associated with arterial oxygen unsaturation, the extreme and persistent tachycardia, and the 10-minute duration of dyspnea are all indications of cardiac disease primarily rather than of intrinsic pulmonary disease. Cardiac disease with pulmonary congestion has been observed to produce similar impairment of performance of these tests. The relative importance of the pulmonary congestion secondary to mitral stenosis and of the hemosiderosis of the lung in the alteration of pulmonary function is impossible to assess. The benign nature of hemosiderosis so far as clinical involvement of lung function is concerned has been pointed out before.[2, 3]

Parker and Weiss[10] have described the changes which occur in the capillaries of the lungs secondary to severe long-standing mitral stenosis. Some of these changes were observed in the present patient, with tortuosity and dilatation of the vessels, and thickening and fibrosis of the adjacent stroma. Occasional septa showed hyalinization and occasional capillary thrombi were seen. These changes are presumably due to the high pulmonary venous and capillary hydrostatic pressure and the slow pulmonary blood flow.

Extravasation of blood into the alveoli is consistently seen in chronic passive congestion of the lungs with the liberation of blood pigments which then are phagocytized by macrophages, producing the so-called "heart failure cell." But ordinarily these cells are diffusely scattered singly or in small groups throughout the lungs and produce no roentgenologic changes. Scott, Park and Lendrum[11] contrast with this usual picture the lesions of pulmonary hemosiderosis which they suggest are the late results of hemorrhage into a terminal air passage. They illustrate by postmortem x-rays the finding of focal hemosiderin in a single portion of the lung. Bronchial vein varicosities have been suggested as the source

of such hemorrhage,[12] but since in this patient many of the hemosiderin deposits were subpleural in location, where the bronchial circulation is ordinarily lacking, the pulmonary vessels seem a more likely source. With long-standing pulmonary hypertension and capillary dilatation diapedesis of red cells may occur into the alveolar spaces and into the interstitial tissue. Whether the extent of this hidden bleeding is associated with the duration and degree of the pulmonary hypertension is an open question. The rarity of the focal changes suggests that some other unknown factor may also be in operation.

Disseminated nontuberculous ossification of the lungs has been reviewed by Wells and Dunlap,[13] and the pathogenesis of these lesions has been outlined by Terplan[14] on the basis of thrombi in the capillaries of the alveolar walls. Such thrombi in capillaries were observed in the present patient. Elkeles and Glynn[15] postulate a specific rheumatic pneumonia rather than long-standing passive congestion as the origin of such ossification. The association of these bony lesions with mitral stenosis is well known. On the other hand, they have been observed also in congestive heart failure from nephrosclerosis.[16] Association with hemosiderosis has not been stressed previously and is perhaps fortuitous.

Summary

A case of mitral stenosis with long-standing exertional cyanosis and a striking radiologic and pathologic picture of pulmonary hemosiderosis is reported. The cyanosis was demonstrated to be due primarily to stasis of the circulation and not the result of poor gas exchange in the lungs.

REFERENCES

[1] Cossio, P., and Berkonsky, I.: The cyanosis in mitral stenosis. Am. Heart J. **17:** 1, 1939.

[2] Pendergrass, E. P., Lame, E. L., and Ostrum, H. W.: Hemosiderosis of the lung due to mitral disease. Am. J. Roentgenol. **61:** 443, 1949.

[3] Hurst, A., Bassin, S., and Levine, I.: Miliary densities associated with mitral stenosis. Am. Rev. Tuberc. **49:** 276, 1944.

[4] Ryder, H. W., and Reineke, H. G.: Pulmonary roentgenographic changes due to mitral stenosis simulating those due to silicosis. Am. Heart J. **29:** 327, 1945.

[5] Sahn, S. H., and Levine, I.: Pulmonary nodules associated with mitral stenosis. Arch. Int. Med. **85:** 483, 1950.

[6] Baldwin, E. deF., Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. Medicine **27:** 243, 1948.

[7] Schafer, P. W., and Shirer, H. W.: An impedance gauging system for measurement of biologic variables. Surgery **26:** 446, 1949.

[8] Hickam, J. B., and Cargill, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation **27:** 10, 1948.

[9] Lundsgaard, C., and Van Slyke, D. D.: Cyanosis. Medicine **2:** 1, 1923.

[10] Parker, F. Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path. **12:** 573, 1936.

[11] Scott, L. D. W., Park, S. D. S., and Lendrum, A. C.: Symposium: Clinical, radiological and pathological aspects of pulmonary hemosiderosis. Brit. J. Radiol. **20:** 100, 1947.

[12] Ferguson, F. C., Kobilak, R. E., and Deitrick, J. E.: Varices of the bronchial veins as a source of hemoptysis in mitral stenosis. Am. Heart J. **28:** 445, 1944.

[13] Wells, H. G., and Dunlap, C. E.: Disseminated ossification of the lung. Arch. Path. **35:** 420, 1943.

[14] Terplan, K. L.: The pathogenesis of tuberous bone formation in the lungs. Am. J. Path. **22:** 632, 1946.

[15] Elkeles, A., and Glynn, L. E.: Disseminated parenchymatous ossification in the lungs in association with mitral stenosis. J. Path. & Bact. **58:** 517, 1946.

[16] Terplan, K. L.: Personal communication.

Chronic Lung Disease, Polycythemia and Congestive Heart Failure

Cardiorespiratory, Vascular and Renal Adjustments in Cor Pulmonale

By Ceylon S. Lewis, Jr., M.D., Arthur J. Samuels, M.D., Merrill C. Daines, M.D., and Hans H. Hecht, M.D.

The relationship of chronic lung disease, congestive heart failure and polycythemia has been examined in 32 subjects including "normal" and "abnormal" controls. The study revealed differences and similarities between cor pulmonale and other types of heart disease. The observations demonstrated a correlation between arterial oxygen tension, as calculated from oxygen content and oxygen capacity, and pulmonary artery pressure. Lowered renal clearance was present in all instances of congestive failure, irrespective of its etiology or of the resting level of cardiac output. It seemed from this preliminary study that bleeding a polycythemic subject with chronic lung disease uncovers a state of oxygen unsaturation that may reflect the conditions which originally led to the development of secondary polycythemia. The possible significance of "oxygen transport" and of altered blood fluidity on the mechanism of heart failure in chronic lung disease is discussed.

SEVERAL studies of cardiovascular function in subjects suffering from chronic lung disease with or without congestive heart failure have been reported recently.[1-6] It is generally assumed that patients with cor pulmonale have an elevated or high resting cardiac output,[4, 6] that regardless of the state of failure, pulmonary artery pressures are elevated, and that arterial unsaturation may be present to an excessive degree. As in other types of heart failure, plasma volume is increased [6, 7] and renal blood flow is grossly impaired.[7, 8, 9]

There is little definite information however, concerning the role of the kidney in "high output" heart failure and the factors leading to polycythemia in such circumstances are obscure. The work to be described was undertaken in an attempt (1) to correlate cardiorespiratory, vascular and renal changes at rest and after exercise in subjects with chronic lung disease with and without polycythemia and with and without signs of congestive failure, and (2) to compare the findings made on these patients with those in normal subjects and in patients with heart failure due to other causes.

Material

Thirty-two subjects were studied. According to clinical findings they fell into five separate groups:

I. The *normal group* consisted of 10 nonhospitalized adult male volunteers 24 to 42 years of age (average 30.4) who were shown to be healthy subjects by physical examination and laboratory tests, including chest x-ray and electrocardiograms.

II. The "*control cardiac*" group consisted of six patients with heart disease of various etiologies. Their ages ranged from 21 to 75 years. All had been in clinical failure in the past and had responded to the usual hospital and outpatient treatment. Five of the six subjects had auricular fibrillation.

III. The "*chronic lung disease*" group consisted of five patients from 35 to 69 years of age, who had pulmonary fibrosis and emphysema of long standing but had not been in cardiac decompensation prior

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Drs. Lewis and Samuels are Fellows in Cardiovascular Research (USPHS). Dr. Daines is a Sandoz Research Fellow.

to the time of the studies. In cases 17, 18, 19, and 21 of tables 1 and 2 there was severe emphysema, and patient 20 had saccular bronchiectasis of all lobes. One of these patients, case 17, was readmitted in congestive failure approximately one month after the studies were completed. This patient and subject 20 had significant polycythemia. Although these patients had not manifested evident congestive heart failure, the presence of heart disease secondary to chronic lung disease, though giving no symptoms at the time of the study, could not be ruled out. Indeed in the two polycythemic subjects there were electrocardiographic changes suggestive of right ventricular "strain."

IV. The six patients comprising the group of *"cor pulmonale" with failure and with polycythemia* ranged from 57 to 72 years of age. All had significant secondary polycythemia, and all had had heart failure in the past, and all had been treated in the hospital by the usual means of bed rest, oxygen, digitalis, low salt diet, and, in some cases, mercurial diuretics. Only case 26 had not been digitalized prior to these studies.

V. The group of *"cor pulmonale" with failure but without secondary polycythemia* is comparable to the preceding group except that polycythemia was not present. The age range in this group of five subjects was 48 to 58 years. All of these patients had, at one time, manifested clinical cardiac decompensation, and in four of the group (cases 28, 29, 30 and 32) the red cell mass had been reduced to normal values by phlebotomy. One patient (case 32) had recently bled from a peptic ulcer.

The diagnosis of cor pulmonale was based on (*a*) the presence of chronic lung disease, by history, physical examination, and chest x-ray; (*b*) right ventricular enlargement by x-ray and electrocardiogram, and (*c*) signs and symptoms of right sided heart failure. It was not possible to rule out the additional diagnosis of arteriosclerotic heart disease in the older subjects.

The clinical status of the three groups of cardiac patients (groups II, IV and V) was approximately the same at the time of the studies.

Methods

Each subject was studied on two successive days. On the first morning renal clearance determinations were performed using para-aminohippurate and inulin.[10, 11] At least three urine collection periods were carried out on each patient and the average results were used.

Following the renal function test, total blood volume and circulating plasma volume were estimated using P^{32} for the former[12] and T 1824 for the latter. The dye dilution curve was obtained by multiple sampling and the plasma dye concentration was determined by the use of a chromatographic column.[13]

Table 1.—*Physical Characteristics of 32 Patients Listed by Diagnosis*

No.	Pt.	Age	Sex	BSA	Kg.	Ht.
			Normal Subjects			
1.	W. J.	28	M	1.78		
2.	C. L.	25	M	2.10	81.0	49.0
3.	R. C.	42	M	1.72	62.6	45.5
4.	A. G.	24	M	1.82		
5.	G. R.	24	M	1.76		
6.	M. O.	39	M	1.89	72.7	48.0
7.	R. S.	25	M	1.80	66.0	52.0
8.	W. H.	28	M	1.96	80.3	48.0
9.	G. W.	36	M	1.72	63.3	47.5
10.	D. M.	33	M	2.01	83.4	45.0
			"Control Cardiacs"			
11.	M. B.	43	M	1.76	67.5	56.0
12.	M. W.	43	F	1.40	43.0	42.0
13.	S. C.	75	M	1.82	71.0	43.0
14.	R. S.	54	M	1.84	71.5	37.0
15.	J. S.	51	M	2.00	67.0	52.9
16.	G. K.	21	M	1.92	65.0	50.0
			Chronic Lung Disease			
17.	W. S.	50	M	1.63	55.3	65.0
18.	C. W.	52	M	1.50	48.1	57.5
19.	H. E.	69	M	1.60	52.7	47.5
20.	D. J.	35	M	1.61	50.0	63.0
21.	K. G.	42	M	1.56	47.3	46.5
			"Cor Pulmonale" with Failure—with Polycythemia			
22.	J. M.	72	M	1.68	59.0	68.5
23.	M. G.	60	M	1.74	67.5	66.0
24.	J. H.	66	M	2.16	95.5	66.0
25.	A. C.	69	M	1.94	78.2	68.0
26.	W. O.	59	M	1.64	54.5	61.0
27.	D. D.	57	M	2.08	90.4	63.0
			"Cor Pulmonale" with Failure—without Polycythemia			
28.	R. S.	56	M	1.68	59.2	59.0
29.	R. C.	58	M	1.72	61.5	46.0
30.	W. P.	56	M	1.56	51.8	49.5
31.	J. M.	48	M	1.58	50.9	51.0
32.	W. S.	50	M	1.64	55.4	39.5

BSA = body surface area.

Ht = volume of packed red cells in per cent of hematocrit reading.

On the following morning, the patient returned in the fasting state for cardiac catheterization. Air

TABLE 2.—*Cardiorespiratory Function, Plasma Volume, and Renal Clearance Data in 32 Cases Listed by Diagnosis*

No.	State	Vent.	O_2 Ext.	O_2 Cons.	Art. O_2	Sat.	A-V	CI	PAP	PV	GFR	RPF	FF
						Normals							
1.	R	2.84	46.3	133	21.8	96.5	4.40	3.0					
	Ex	3.70	56.1	208	22.2	98.2	4.80	4.4					
	R	3.43	47.6	163	21.6	95.6	3.60	4.5					
2.	R	3.14	53.0	166	18.0	96.8	3.80	4.4	17	3000	115	546	.21
	Ex	4.00	58.4	234	18.5	99.5	4.10	5.7					
	R	2.43	61.0	147	17.9	96.2	3.80	3.9					
3.	R	3.92	39.2	154	18.1	95.7				2650	95	623	.15
	Ex	4.50	48.0	216	17.9	94.7							
4.	R	2.25	58.5	132	17.5	89.7	4.50	2.9					
	Ex	3.35	66.9	224	18.1	89.6	5.0	4.5					
	R	2.64	60.4	159	17.6	89.2	4.50	3.5					
5.	R	4.04	39.5	159	20.2	92.0	4.10	3.9					
	Ex	5.28	45.7	241	20.4	92.6	5.50	4.4					
	R	5.05	36.0	182	21.0	95.5	5.70	3.2					
6.	R	2.77	37.2	103	17.1	87.2	3.80	2.7		2900	107	595	.18
	Ex	4.95	41.8	200	17.2	92.7	3.60	5.8					
	R	3.72	37.8	141	18.8	95.9	5.50	2.6					
7.	R	2.37	56.0	133	18.8	95.9	4.10	3.2	14	3375	156	886	.17
	Ex	4.95	58.6	291	19.4	99.2	5.53	5.25	16				
	R	3.23	58.5	189	19.1	97.6	4.04	4.7	15				
8.	R	3.39	50.0	169	15.7	93.5	3.35	5.05	20	3625	120	576	.21
	Ex	5.20	58.0	302	17.5	100.0	5.33	5.7	22				
	R	3.90	52.0	203	16.6	95.4	3.72	5.46	20				
9.	R	1.85	56.0	103	14.3	92.7	3.80	2.73		2825	134	714	.18
10.	R	2.64	45.0	118	17.4	93.5	5.40	2.19	14	2675	96	534	.18
	Ex	6.46	42.0	271	17.6	94.6	5.70	4.75	18				
Avg.	R	2.92	48.1	137	17.9	92.1	4.14	3.34	16	3007	118	639	.18
	Ex	4.71	52.8	243	19.8	94.5	4.95	5.06	18				
	R	3.49	50.5	169	18.9	94.5	4.41	3.98	18				

Abbreviations

R = Rest
Ex = Exercise
Vent* = Ventilation L./min./M.²
O_2Ext = Oxygen extraction ml./L. ventilation
O_2Cons* = Oxygen consumption ml./min./M.²
Art. O_2 = Arterial oxygen content vol. %
Sat. = Arterial oxygen saturation %
A-V = Arteriovenous oxygen difference vol %
CI = Cardiac output L./min./M.²
PAP = Pulmonary artery pressure mm. Hg
PV = Plasma volume ml.
GFR = Glomerular filtration rate
RPF = Renal plasma flow
FF = Filtration fraction

* Corrected to 0 degrees t, vapor pressure and 760 mm. Hg

All subjects were sedated.

It is recalled that at Salt Lake City (4500 feet) barometric pressures average 640 mm. Hg and pO_2 135 mm. Hg.

TABLE 2—*Continued*

No.	State	Vent.	O_2 Ext.	O_2 Cons.	Art. O_2	Sat.	A-V	CI	PAP	PV	GFR	RPF	FF
						"Control Cardiacs"							
11.	R	2.90	56.8	165	20.2	87.1	6.40	2.6		2825			
	Ex	5.40	61.5	332	20.2	87.1	9.20	3.6					
	R	2.56	62.2	159	19.7	84.9	6.60	2.4					
12.	R	2.67	31.1	83	15.5	92.8	5.60	1.49	32	2250	67	299	.22
	Ex	3.52	37.5	132	15.9	95.2	7.20	1.84					
	R	3.10	35.5	107	15.0	89.2	4.80	2.22					
13.	R	3.82	37.0	142	13.8	83.1	4.60	3.08	43	4600	56	165	.34
	Ex	5.88	38.0	224	12.0	72.3	6.90	3.24	53				
	R	4.04	37.0	149	11.5	69.3	4.30	3.46	45				
14.	R	1.18	58.9	70	16.8	92.8	5.80	1.20		3600	35	136	.26
	Ex	3.70	47.0	174	17.1	96.2	7.50	2.32					
	R	1.58	47.9	76	18.0	99.4	7.20	1.05					
15.	R	2.38	39.0	93	16.7	83.9	5.30	1.74	21	3150	108	388	.28
	Ex	5.20	44.8	233	18.5	93.0	8.40	2.77	28				
	R	3.08	37.2	115	17.5	87.9	5.50	2.09	22				
16.	R	3.27	35.2	115	14.4	90.0	5.60	2.06	50	3150	96	354	.27
	Ex	5.83	35.7	206	16.3	100.0	8.50	2.37	69				
	R	4.06	34.5	140	15.6	97.5	6.20	2.12	48				
Avg.	R	2.70	43.0	111	16.2	88.3	5.55	2.03	37	3263	72	268	.27
	Ex	4.92	44.1	217	16.7	91.0	7.95	2.69	50				
	R	3.07	42.4	124	16.2	88.1	5.76	2.22	38				
						Chronic Lung Disease							
17.	R	2.88	46.3	134	18.0	75.6	3.60	3.70	22	2550	111	488	.22
	Ex	4.53	43.8	198	18.2	76.5	4.60	4.20	30				
	R	3.19	41.5	133	18.0	75.6	3.60	3.70	23				
18.	R	3.70	36.5	137	12.8	56.9	2.40	5.70	25	2125	127	800	.16
	Ex	4.40	33.9	150	12.8	56.9	3.30	4.50	30				
	R	3.61	44.0	159	15.4	68.4	4.30	3.70	22				
19.	R	5.13	33.0	169	15.4	82.8	4.80	3.52	43	2725	89	515	.17
	Ex	7.0	33.5	234	13.5	72.6	5.10	4.59	51				
	R	5.94	31.2	186	17.3	93.0	4.30	4.34	45				
20.	R	5.10	32.0	163	17.5	71.1	6.90	2.37	29	1825	92	440	.20
	Ex	6.74	41.0	276	18.7	76.0	6.90	4.01	39				
21.	R	4.94	35.8	141	14.9	90.3	4.10	3.46	42	2775	99	500	.19
	Ex	5.30	38.9	199	14.6	88.5	5.20	3.96	56				
	R	3.88	35.2	137	15.1	91.5	4.60	2.98	41				
Avg.	R	4.35	36.7	149	15.7	75.3	4.36	3.75	32	2400	104	549	.10
	Ex	5.59	38.2	211	15.6	74.1	5.06	4.25	41				
	R	4.16	38.0	154	16.5	82.1	4.20	3.68	33				

TABLE 2—*Concluded*

No.	State	Vent.	O_2 Ext.	O_2 Cons.	Art. O_2	Sat.	A-V	CI	PAP	PV	GFR	RPF	FF
						"Cor Pulmonale" with Failure—with Polycythemia							
22.	R	4.54	32.0	145	18.7	67.7	5.20	2.80	39	2925	89	280	.31
	Ex	5.0	25.0	200	18.1	65.6	4.60	4.30	50				
	R	3.78	33.8	128	20.0	72.5	3.90	3.30	39				
23.	R	3.51	39.3	137	13.7	64.0	2.40	5.73	49	3225	83	249	.33
	Ex	4.51	43.5	196	12.5	58.4	6.0	3.32	69				
	R	3.45	40.0	138	14.6	68.2	2.30	6.01	51				
24.	R	2.64	53.0	140	16.3	67.6	7.40	1.90	46	3375	77	246	.31
	Ex	4.40	46.0	202	18.0	74.7	6.20	3.24	55				
	R	7.0	44.0	227	18.6	77.2	5.90	3.84	49				
25.	R	3.04	37.0	112	19.0	77.9	6.50	1.73	56	2100	64	250	.26
	Ex	5.37	30.0	161	18.0	73.8	10.70	1.51	65				
	R	3.91	29.7	117	19.0	77.9	6.50	1.80	57				
26.	R	2.44	37.0	91	17.2	77.1	4.80	1.89	30	2500	83	315	.26
	Ex	3.78	41.8	158	16.5	74.0	6.40	2.46	40				
27.	R	2.46	44.5	110	11.6	51.3	5.10	2.15	45	2575	60	207	.29
	Ex	2.55	45.0	115	14.6	64.6	7.40	1.56	54				
	R	2.57	38.0	98	13.6	60.2	2.90	3.38	49				
Avg.	R	3.11	40.5	123	16.9	67.6	5.23	2.70	44	2783	76	258	.20
	Ex	4.27	38.6	172	16.3	68.5	6.88	2.73	56				
	R	4.14	37.1	142	17.2	71.2	4.30	3.67	49				
						"Cor Pulmonale" with Failure—without Polycythemia							
28.	R	3.12	43.4	135	10.5	53.0	3.10	4.40		2750	53	269	.20
	Ex	3.49	47.0	164	9.1	45.9	4.60	3.60					
	R	2.81	42.3	119	11.4	57.6	2.80	4.20					
29.	R	4.23	36.0	152	12.4	66.7	6.00	2.60	31	2950	131	430	.30
	Ex	5.2	37.1	193	9.4	50.5	3.70	5.20	61				
	R	3.12	35.3	110	12.0	64.5	4.00	2.80	47				
30.	R	3.91	36.0	140	8.7	51.2	4.30	3.30		3000	72	247	.29
	Ex	5.70	26.6	192	9.4	55.3	6.20	3.10					
	R	3.65	36.2	131	10.2	60.0	5.60	2.40					
31.	R	3.67	28.0	104	12.2	68.5	4.10	2.53	69	3000	86	269	.32
	Ex	6.26	30.0	186	12.7	71.3	6.30	2.95	81				
	R	4.18	29.0	120	14.6	82.0	4.60	2.62	62				
32.	R	3.72	39.5	147	6.5	47.8	3.85	3.81	55	3000	51	270	.19
	Ex	6.53	35.5	232	6.70	49.3	4.19	5.54	68				
	R	4.31	37.0	159	6.5	47.8	3.58	4.44	52				
Avg.	R	3.73	36.6	136	10.1	57.4	4.27	3.33	52	3140	79	297	.26
	Ex	5.44	35.2	193	9.5	54.5	5.00	4.08	70				
	R	3.61	35.0	128	10.9	62.4	4.12	3.29	54				

samples were analyzed by means of a Haldane-Henderson-Bailey apparatus or a Pauling oxygen analyzer (Model E). Blood gases were determined by the method of Neill and Van Slyke. In vitro saturation was obtained by a tonometer method and checked against colorimetric hemoglobin determinations based on standards using crystallized hemin. The slight inaccuracy of the tonometer procedure is recognized.

Cardiac output was determined at rest, immediately following mild exercise (weight lifting), and 10 minutes after cessation of exercise. Pulmonary artery pressures were measured directly by means of a Statham Strain Gage or a Sanborn Electromanometer. Mean pressure, when not obtained by integration, was calculated by adding one-third of the pulse pressure to the diastolic pressure.[15]

Right or left heart work was calculated by the formula of Dexter and co-workers,[16] pulmonary and total peripheral resistance by the formula of Cournand, Riley and others.[17]

"Oxygen extraction" was calculated as milliliters oxygen consumed per liter of air ventilated.[18, 19]

Results

Pulmonary Ventilation, "Oxygen Extraction," Oxygen Consumption

All the patients with chronic lung disease showed somewhat higher values for pulmonary ventilation than the subjects composing the normal or the "cardiac control" group, but they were not able to increase their ventilation as well with exercise. In the group with chronic lung disease, cor pulmonale and polycythemia (group IV), the ventilation volume failed to return to the resting level 10 minutes after mild exertion. Irrespective of the presence of congestive failure and of polycythemia, all patients with chronic lung disease lacked the ability to increase their oxygen consumption on exercise in the normal manner (table 2).

"Oxygen extraction" (milliliters oxygen consumed per liter ventilated) was relatively normal at rest in all five groups. All the patients with heart disease, as well as those with chronic lung disease, failed to increase their oxygen extraction even on mild exertion (table 2). This is considered a sign of pulmonary inefficiency and it is of interest in this respect that oxygen extraction and its response to exercise was normal in four subjects with polycythemia vera.

Arterial Oxygen Saturation and Arteriovenous Difference

The arterial oxygen saturation and the calculated oxygen tension in the patients with cor pulmonale and in those with chronic lung disease alone was significantly lower than in those making up the normal or "cardiac control" groups (table 2). The arteriovenous difference was high in the "cardiac control" group and in patients with cor pulmonale and secondary polycythemia. The arteriovenous difference in the normal subjects, in patients with chronic lung disease, and in those forming the group with cor pulmonale without polycythemia was strikingly similar at rest and on exercise. In the "cardiac control" group and in the patients with heart disease and polycythemia, the per cent increase in arteriovenous difference on exertion was significantly greater than in the other groups. In the few cases of "cor pulmonale" without polycythemia there was observed an unusually low arterial oxygen content, which appeared to be out of proportion to the difference in the volume of packed red cells. The severe oxygen deficiency apparently characteristic of the group was also observed in subjects who were studied both at high and low levels of volume of packed red cells.

Cardiac Output

The average resting cardiac index fell within the normal range in all groups except the "control cardiacs." Higher than normal outputs were encountered in only two instances, one with and one without polycythemia (cases 18 and 23, table 2). Following mild exercise, cardiac output increased approximately 60 per cent in the normal group. Less than normal responses to exercise were characteristic for all other groups. This was particularly striking in the subjects with cor pulmonale and polycythemia. Three of the six patients of this group responded with a fall in output on exercise. The group with polycythemia was further characterized by a late rise in output in the postexercise period, which occurred in five of the six patients (fig. 1). It appears from this group of patients that the cardiac response to exercise is particularly impaired when polycythemia is present.

Pressures

Arterial pressures were normal in all patients of this series. The pulmonary artery pressure was elevated in all but the normal group; patients with evidence of congestive failure tended to have higher pressures than those with chronic lung disease alone. On exercise, the pulmonary artery pressures rose in all abnormal groups. The detailed relationship between arterial unsaturation, pulmonary disease, congestive failure, pulmonary artery and "pulmonary capillary" pressures will be the subject of a separate report[21] (fig. 2).

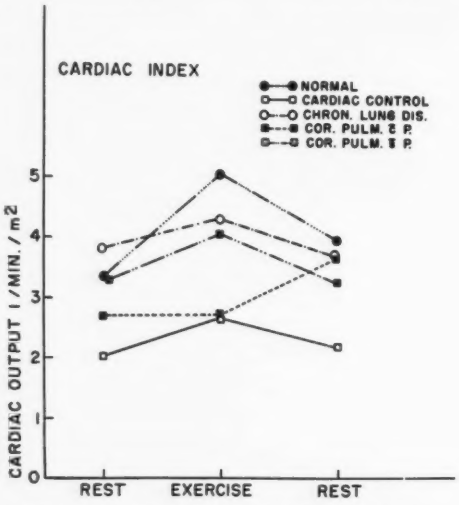

FIG. 1. *Cardiac Index.* Low output in "compensated" cardiac control group, "high output" in all other groups examined. Lack of response to exercise with postexercise rise in subjects with cor pulmonale and polycythemia but not in nonpolycythemic cor pulmonale.

Pulmonary Resistance

The calculated "pulmonary resistance" was increased in subjects with chronic lung disease. This calculated value was still higher in the groups with lung disease that had been in congestive failure, either because of a lower cardiac output or because of further increase of pulmonary artery pressure. The group with cor pulmonale and polycythemia who had failed to respond with an increased cardiac output following exercise therefore demonstrated a sharp increase in pulmonary resistance on effort (table 3).

Heart Work

"Right heart work" expressed in kilogrammeters per minute per square meter of surface area[16] was significantly increased in all groups when compared with normal volunteers. The "cardiac control" group and the subjects with chronic lung disease who had not been in failure demonstrated a normal response to exercise and differed from the normals only in that the work load was somewhat increased, presumably on the basis of increased pulmonary resistance. In cor pulmonale with polycythemia, the work load continued to rise following exercise, which is a reflection of the peculiar behavior of the cardiac output in this group. When polycythemia was artificially corrected, the work load on the right heart nevertheless was high and increased remarkably on exertion. This appears to be the result of generally higher pulmonary resistance in this group (fig. 3). Left heart work, as illustrated in figure 3*b*, reflects the changes in cardiac output discussed above.

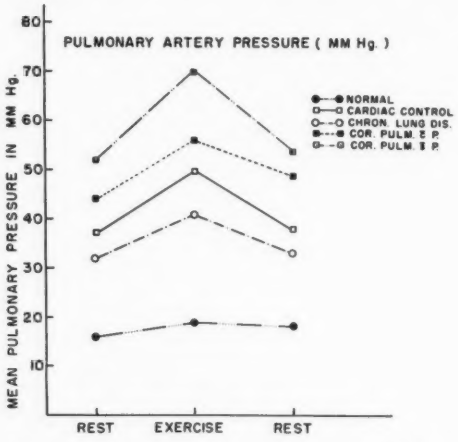

FIG. 2. *Pulmonary Artery Pressure.* Highest pulmonary artery pressures in the group with lowest oxygen content: the subjects with cor pulmonale who are not polycythemic.

By using these work load figures in the formula

$$\frac{\textit{Left Heart Work}}{\textit{Right Heart Work}}$$

a value is obtained which represents the ratio of the work performed by each side of the

heart. In normal subjects, this figure is 5.5 at rest, indicating that the external work performance of the left ventricle is over five times as great as that of the right. With exercise, this figure falls, which indicates that the right heart work load is increased in greater proportion than the left. In the "cardiac control" of patients with chronic lung disease who had not been in congestive heart failure, and in subjects with polycythemia vera (not here reported) the clearance figures were essentially normal. The filtration fractions of the patients with heart disease were moderately elevated (fig. 4). Figure 4 emphasizes the essential simi-

TABLE 3.—*Total Pulmonary Resistance (dynes/sec./cm.⁵)*

Groups	Rest	Exercise	% Change	Rest	% Change
Normal	189 (148–255)	148 (135–158)	−24	147 (143–150)	0
"Control cardiacs"	701 (481–1165)	770 (403–1190)	+10	645 (420–945)	−16
Chronic lung disease	473 (234–624)	494 (353–726)	+4	463 (306–706)	−6
"Cor pulmonale" with failure with polycythemia	811 (393–1332)	1001 (548–1781)	+23	658 (392–1302)	−34
"Cor pulmonale" with failure without polycythemia	882 (563–1378)	842 (542–1383)	−5	854 (571–1200)	+1

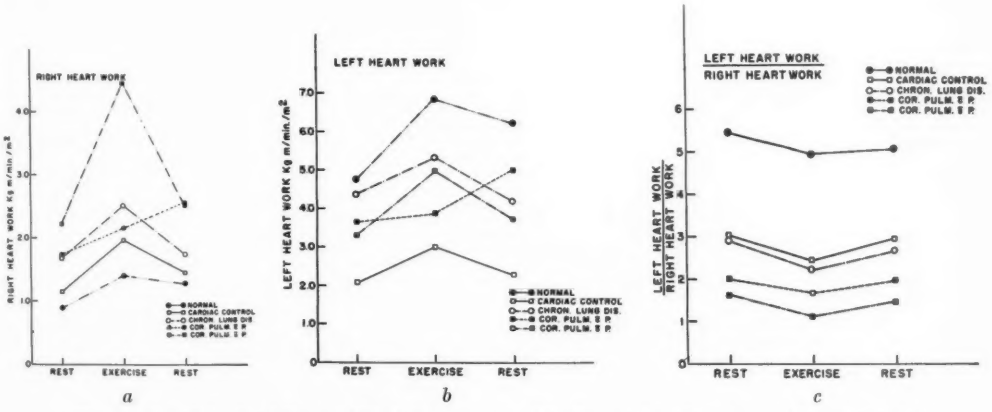

FIG. 3*a*, *b*, *c*. *Calculated External Work Performance of the Heart* (viscosity not considered). See text.

group and in subjects with chronic lung disease, this figure was lower than in the normals (3.03 and 3.23 respectively). In the patients with cor pulmonale, the figure was still further reduced, approaching unity and expressing a further increase in the external work load of the right heart compared with the left (fig. 3*c*).

Renal Clearances

There was a significant reduction in the renal plasma flow and in glomerular filtration rate in the patients who had heart disease, irrespective of etiology, level of cardiac output, or polycythemia. On the other hand, in the group larity of the renal changes in all groups with heart disease.

Circulating Blood Volume

Table 4 gives the average values for the so-called total circulating plasma volume. Plasma volumes were high in the "control cardiacs" and in the subjects that had been bled. They were lower, on the average, in the patients with significant polycythemia. The calculated total blood volume appeared to be high in all groups other than the normals. As expected, the figures for total blood volume using radioactive phosphorus were lower by about 15 per cent than

the estimated values based on the plasma volume and the hematocrit reading. No consistent difference between the two methods was found and therefore no correction factor could be applied to obtain equal results for the two methods.

Correlations

1. When the values for cardiac output are divided by the estimated total circulating blood volume, it can be shown that in normal subjects, the per cent of the blood volume pumped by the heart per minute is slightly over 100.

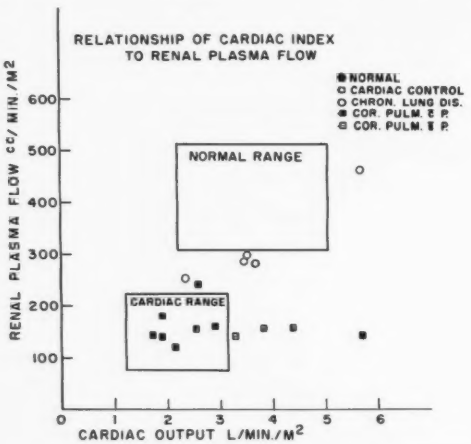

FIG. 4. *Renal Plasma Flow (para-aminohippurate clearance) in Cor Pulmonale.* Irrespective of resting cardiac output renal plasma flow is reduced and indistinguishable from that in other types of heart failure.

If any value can be attached to the determinations of circulating blood volume, this indicates that a volume equal to the estimated volume of blood passes through the heart once per minute. In this series, the per cent of total blood volume circulated per minute was 108, 114 and 90 in the normal volunteers, the chronic lung disease group and in patients with cor pulmonale without polycythemia, respectively. It was significantly reduced in the "control cardiacs" and in the subjects with cor pulmonale and polycythemia (61 and 60 respectively) (table 4).

2. When renal plasma flow is compared with the cardiac index, it is seen that, in general, the renal clearance values were low in subjects with cor pulmonale irrespective of cardiac output or the presence or absence of polycythemia. In figure 4, the range of cardiac output and of renal plasma flow is plotted for the normal subjects and for the cardiac control group. Subjects with chronic lung disease or cor pulmonale are represented by individual points. It is seen that in only 3 of the 11 patients with cor pulmonale was the cardiac output slightly lowered; yet in all, the renal values were in the cardiac failure range.

3. Renal function may be expressed in terms of per cent of the circulating plasma volume flowing through the kidney per minute. In the subjects without heart disease, 23 per cent of the circulating plasma flowed through the kidney per minute. In this series, all subjects with heart disease demonstrated a sharp reduction in the volume flow, averaging 10 per cent irrespective of etiology or the presence of polycythemia.

Characteristics of the Groups

The four abnormal groups differed in several aspects from the group of normal volunteers. It is recognized (*a*) the small number of subjects examined precludes definitive statements and (*b*) that the volunteers cannot be considered a "true" control series, as the physical characteristics and the ages were not identical with those of the abnormal groups. The separation of the patients examined in this series into four different groups was made on clinical grounds, and it is likely that some overlapping occurred. Naturally the factors in patients with chronic lung disease leading to the development of polycythemia, and to the eventual onset of congestive failure, must be present for some time before these overt manifestations become evident.

The group designated as "cardiac controls" demonstrated a decreased cardiac output, mainly on the basis of an increased arteriovenous oxygen difference.[2, 23] The calculated external work performance of the left ventricle was somewhat decreased, while that of the right ventricle increased as pulmonary artery pressure rose. The glomerular filtration rate and renal plasma flow were decreased and the filtration fraction was high. The circulating

plasma volume was increased but the per cent of plasma flowing through the kidney was less than one-half the normal value. This group of patients who, with one exception, were not in failure at the time of the studies demonstrated all the findings of the low output group. These observations are in accord with those of Merrill and others.[2, 23, 24]

Subjects with chronic lung disease but without heart failure were characterized by moderate arterial unsaturation and a slightly increased ventilation rate. Cardiac output was normal and renal function was within the low normal range. The right heart work was increased in proportion to an observed increase in pulmonary artery pressure. It is likely that this had resulted in right ventricular hypertrophy which in fact was demonstrated electrocardiographically in two subjects of this group. Since overt congestive failure must be considered only a late manifestation of an insufficiently functioning heart the transition from chronic lung disease to chronic lung disease with "cor pulmonale" is gradual and the presence or absence of right ventricular hypertrophy alone cannot be considered adequate for the diagnosis of cor pulmonale.

In the subjects with chronic lung disease who had been in heart failure and in whom the diagnosis of cor pulmonale was never in doubt, many features of the "cardiac control" group were encountered, namely, increased arteriovenous differences, particularly on exercise, decreased external work performed by the left ventricle and increased right heart work, the latter caused by elevated pulmonary artery pressure. Renal function was depressed to a degree comparable to that observed in the "cardiac control" group. On the other hand, this group differed from the ordinary types of heart disease by the presence of marked arterial unsaturation and relatively normal resting cardiac output which, however, failed to increase with exercise. "Secondary" polycythemia was prominent in this group.

In the group of subjects in whom the polycythemia had been corrected, arterial unsaturation was usually more striking and pulmonary artery pressures in three subjects were higher than in the previous group. As the cardiac output, on the whole, increased, the right heart work load rose excessively (fig. 3a). Renal clearance values were similar to those found in the other heart failure groups. In spite of a reduction in red cell mass, a corresponding increase in circulating plasma volume presumably caused the total calculated circulating blood volume to remain unchanged. The differences between these two cor pulmonale groups are of considerable interest, since the severity of the lung disease did not appear to differ.

TABLE 4.—*Blood Volume Data in cc./Kg.*

Groups	Plasma Vol. (T 1824)	Tot. Bl. Vol. (T 1824 + Ht.)	Tot. Bl. Vol. (P^{32})	$\frac{RPF^*}{PV}$	$\frac{CO\ \dagger}{TBV}$
Normal	42 (32.1–51.1)	81 (58–107)	71 (64–81)	23 (18–25)	108 (82–156)
"Control cardiacs"	51 (41.9–64.8)	96 (80–114)	82 (67–117)	9 (4–14)	61 (32–89)
Chronic lung disease	47 (36.5–58.5)	105 (90–132)	87 (76–108)	21 (16–33)	114 (77–172)
"Cor pulmonale" with polycyth.	39 (26.8–49.6)	114 (77–158)	87 (63–113)	10 (8–13)	60 (41–105)
"Cor pulmonale" without polycyth.	56 (46.5-64.2)	111 (90–120)	88 (83–90)	9 (7–11)	90 (60–126)

* Relation of renal plasma flow to plasma volume, expressed in per cent of circulating plasma (see text).

† Per cent of circulating total blood volume passing through the heart per minute (see text). CO = cardiac output.

Discussion

It seems apparent from the results presented that in our groups with chronic lung disease cardiac output was adequate though renal clearance was impaired once congestive failure

had occurred. The kidney appears to be a more sensitive indicator of cardiac efficiency than does cardiac output alone, at least when studied at rest and during moderate exercise. On the other hand, not reflected in relatively gross measurements of renal function are the obvious differences in vascular adjustments apparent when a "low output failure group" is compared with cases of "cor pulmonale" or at least with a group in whom impairment in pulmonary circulation is a predominant factor.

The finding of reduced renal plasma flow in cor pulmonale with essentially normal cardiac output and no obvious increase in the metabolic needs of these patients has been reported before.[7, 8, 9] Merrill[24] related the lowered renal plasma flow to cardiac output and has postulated that a decreased cardiac output serves as a stimulus for a decrease in renal blood flow. In our series of patients with heart failure secondary to lung disease, the resting outputs were normal, but it is admitted that in several subjects with polycythemia the output rose inadequately on minor exercise. It may be argued that, in those patients, the average output during daily activities is still below normal and is inadequate to meet body needs. On the other hand, renal function was equally disturbed in those patients in whom polycythemia had been corrected by bleeding, and who demonstrated an essentially normal cardiac output and exercise response. It is possible therefore, that in cor pulmonale the level of cardiac output is not the sole factor controlling renal blood flow.

The primary difference between patients with heart failure on the basis of predominant cor pulmonale and subjects with congestive failure of the "low output" type is of course the presence of low arterial oxygen content with a low partial pressure of oxygen in the arterial blood. If cardiac output is correlated with arterial oxygen content, a figure can be obtained which expresses in milliliters the oxygen transported per minute. (*Oxygen transport* per minute per square meter of body surface equals arterial oxygen in volumes per 100 ml. $\times$ 10 $\times$ cardiac index.) This product should be the same whether cardiac output is low and arterial oxygen is normal ("low output" group), or cardiac output is normal and arterial oxygen is low (cor pulmonale). Therefore, oxygen transport figures (oxygen delivered) should be similar in all types of congestive failure where the metabolic needs of the body have not been increased. In the normal volunteers and in the subjects with chronic lung disease, but without heart disease, "oxygen transport" was calculated as being 597 and 574 ml. per minute per square meter of body surface, respectively, as compared with 329, 420 and 326 in the three groups in which heart failure had occurred. The oxygen supply to the tissues is dependent on the partial pressure of oxygen prevailing at the exchange site *and* the amount offered per unit of time. This in turn depends on the flow of blood to the tissues as governed by the vascular lumen and the amount of oxygen carried by the blood, the oxygen transport. It is tempting to speculate that "oxygen transport" rather than cardiac output *per se* or arterial saturation *per se* which is known not to influence renal clearances, at least during short periods of anoxia,[30] may serve as a factor in controlling renal plasma flow in congestive failure of various kinds.

The low values of arterial oxygen content, here associated with lowered oxygen tension, correlate with high pulmonary artery pressures. This inverse relationship has been observed by several groups and was noted in subjects during breathing of 100 per cent oxygen, whether they were polycythemic or not or whether they were suffering from lung disease or not.[21] In subjects who had been bled (group V) the arterial saturation was unchanged or tended to be at lower levels than in the group that was examined while polycythemic. If arterial saturation is lower, pulmonary artery pressure will be higher and the load on the right ventricle greater (fig. 3*a*), and this in the face of an obviously decreased oxygen supply to the heart.

These preliminary observations on patients with chronic lung disease, heart failure and polycythemia throw doubt on the wisdom of phlebotomizing moderately polycythemic subjects in whom the factor of viscosity is not of primary importance. It is also possible that this group reflects the status of patients with

chronic lung disease immediately prior to the development of polycythemia and of heart failure. From our figures, it would appear that, in chronic lung disease, an arterial saturation of about 70 per cent (35 mm. Hg pO_2) would eventually lead to the development of secondary polycythemia. It is of interest that this represents the approximate level of unsaturation above which polycythemia disappears in patients subjected to surgical correction for cyanotic congenital heart disease.[32] If the critical value for the development of polycythemia is assumed to lie at 70 per cent, subject number 18 of table 2 with an arterial unsaturation of 57 per cent and a fall in cardiac output on exercise, would represent the final stage before the development of polycythemia. Subject 17, who was polycythemic, would represent a patient that had responded to his low arterial oxygen tension but had not yet gone into heart failure. As we have pointed out, this patient developed congestive failure within four weeks following these observations.

Blood flow through an area is dependent on cardiac output ("perfusion pressure"), the caliber of the vascular bed ("hindrance") and the specific physical properties of the blood which determine its behavior during pulsatile flow ("viscosity"). The estimation of "resistance" and "work" now frequently used in conjunction with direct determination of vascular pressures and blood flow in human subjects must take into account resistance offered by the shearing forces existing between blood and blood vessels, commonly expressed as "viscosity," or its reciprocal "fluidity." These in turn depend on the size of the vessel, the behavior of the suspension of cells in plasma at determined flow rates, the rate of flow itself, and the character of the flow—whether streamlined or turbulent.

The hemodynamic properties of the blood in the major part of the circulation are those characteristic of "pseudoplastic" fluids which flow even when the smallest pressure is applied and increase their flow rates disproportionally faster as the propelling force increases.[33] At least in larger vessels blood will flow at extremely low cardiac output and as the output rises its flow will increase to a far greater degree than if water or plasma were the sole circulating substances.

It is characteristic for pseudoplastic fluids to exhibit high viscosity at slow rates of flow and low viscosity at rapid flow so that it may be argued that the influence of viscosity will be greater in subjects in heart failure with low outputs and delayed circulation times than in those with high cardiac outputs and rapid circulation. Increase in resistance, such as observed in the pulmonary vascular bed in anoxic states, increases relative viscosity of blood considerably.[34]

Changes in cardiac output and changes in pulmonary vascular "tone" occasioned by different degrees of arterial oxygen saturation at rest and at exercise and at various volumes of red cells will independently influence blood viscosity and this in turn will alter total pulmonary resistance and right ventricular work load and work performance in an as yet unpredictable manner.

It is agreed that an increased cell concentration raises the "apparent" viscosity of the blood when measured by comparing rates of blood flow with that of water or saline in rigid glass tubes[35] or in isolated vascular regions.[36] Recent observations seem to indicate that the changes are almost linear at physiologic perfusion pressures.[33] These observations, however, afford no means by which the influence of polycythemic blood on cardiac load in vivo can be estimated. However, it may be argued that the actual differences in workloads between subjects with and without polycythemia may be less than presented here, although from available evidence[34, 35] the influence of viscosity may not be large enough to invalidate the statements made.

Summary

1. In 32 subjects observations were made on cardiac output, vascular pressures, plasma and total blood volume, and renal clearance. For the purpose of further analysis, the subjects were separated into five clinical groups: (1) normal volunteers, (2) "cardiac controls," (3) patients with chronic lung disease not in heart failure, (4) patients with chronic lung disease and polycythemia who had been in congestive

failure in the past (cor pulmonale), and (5) patients with chronic lung disease and cor pulmonale in whom secondary polycythemia was absent at the time of the study.

2. In the subjects with heart failure secondary to chronic lung disease cardiac output at rest fell within the normal range but renal function was impaired and the filtration fraction was elevated.

3. The patients with cor pulmonale and polycythemia lacked the ability to increase cardiac output adequately on exercise. This appeared partially corrected in the nonpolycythemia group, almost all of whom had been bled. Renal clearance remained unchanged, however, and the pulmonary artery pressure of three nonpolycythemic subjects with cor pulmonale was excessively high.

4. In the group with cor pulmonale where polycythemia had been corrected, arterial unsaturation was more severe and pulmonary artery pressure higher than in polycythemic subjects. Since the cardiac output rose, this indicated that the calculated external work performance of the right ventricle was sharply increased.

5. It is postulated that this stage of severe arterial unsaturation with low oxygen tension of arterial, mixed venous and bone marrow blood and with an excessive load on the right ventricle represents a state of chronic lung disease which leads to the development of (*a*) polycythemia and (*b*) right ventricular failure. Polycythemia and heart failure show a positive correlation but one is not necessarily dependent on the other and either one or both may develop as the result of severe chronic pulmonary vascular disease.

6. Alterations in cardiac output alone do not necessarily represent the only means by which renal function is decreased in heart failure. In subjects with cor pulmonale, oxygen delivered, expressed as the product of arterial saturation and cardiac output ("oxygen transport"), may be another determining factor.

7. Removal of blood in patients with "secondary" polycythemia and chronic lung disease may increase cardiac output but it would seem to further impair certain cardiovascular adjustments and occasionally results in severe oxygen deficiency.

8. The possible influence of certain rheological properties of the blood (viscosity) on peripheral and pulmonary "resistance" and on cardiac "work load" is discussed.

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REFERENCES

[1] Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. J. Clin. Investigation **25:** 639, 1946.

[2] Hickam, J. B., and Cargill, W. H.: Effects of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation **27:** 10, 1948.

[3] Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A.: Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. Am. J. Physiol. **152:** 372, 1948.

[4] McMichael, J.: Pharmacology of the Failing Human Heart. Springfield Ill., Charles C Thomas, 1950.

[5] Zimmerman, H. A.: A study of the pulmonary circulation in man. Dis. Chest **20:** 46, 1951.

[6] Harvey, R. M., Ferrer, M. I., Richards, D. W., Jr., and Cournand, A.: Influence of chronic pulmonary disease on the heart and circulation. Am. J. Med. **10:** 719, 1951.

[7] Lewis, C. S., Samuels, A. J., Daines, M. C., Carlisle, R., Ukradyha, F., and Hecht, H. H.: Cardiovascular-renal adjustments in cor pulmonale. Am. J. Med. **10:** 765, 1951.

[8] Davies, C. E. and Kilpatrick, J. A.: Renal circulation in "low output" and "high output" heart failure. I. Clin. Sc. **10:** 53, 1951.

[9] Fishman, A. P., Maxwell, M. H., Crowder, C. H., and Morales, P.: Kidney function in cor pulmonale. Circulation **3:** 703, 1951.

[10] Smith, H. W.: Lectures on the Kidney. Lawrence University Extension Division, University of Kansas, 1943.

[11] Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease. New York, The Commonwealth Fund, 1944.

[12] Reid, A. F., and Orr, M. K.: A rapid method for determining blood volumes by the use of P32 labeled red cells. J. Clin. Investigation **29:** 313, 1950.

[13] Hecht, H. H.: Unpublished observations.

[14] —, Osher, W. J., and Samuels, A. J.: Cardiovascular adjustments in subjects with organic heart disease before and after conversion of atrial fibrillation to normal sinus rhythm. J. Clin. Investigation **30:** 647, 1951.

[15] Scheinberg, P., and Stead, E. A., Jr.: The cerebral blood flow in male subjects as measured by the nitrous oxide technique. J. Clin. Investigation **28:** 1163, 1949.

[16] Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K.: Studies of pulmonary circulation in man at rest. Normal variations and interrelations between increased pulmonary blood flow, elevated pulmonary arterial pressure and high pulmonary "capillary" pressures. J. Clin. Investigation **29:** 602, 1950.

[17] Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lauson, H. D., Gregerson, M. I., and Richards, D. W., Jr.: Studies of the circulation in clinical shock. Surgery **13:** 964, 1943.

[18] Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Studies in congenital heart disease. I. Bull. Johns Hopkins Hosp. **80:** 107, 1947.

[19] Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency. Discussion of the physiological classification and presentation of clinical tests. Am. Rev. Tuberc. **44:** 26, 1941.

[20] Samuels, A. J., Hecht, H. H., Daines, M. C., and Lewis, C. S.: The oxygen content of sternal bone marrow and its relation to polycythemic states, to anemia, and to heart failure. Am. J. Med. **12:** 108, 1952.

[21] Daines, M. C., Lewis, C. S., Samuels, A. J., and Hecht, H. H.: To be published.

[22] Davies, D. F., and Shock, N. W.: Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J. Clin. Investigation **29:** 496, 1950.

[23] Stead, E. A., Jr., Warren, J. V., and Brannon, E. S.: Cardiac output in congestive heart failure. Am. Heart J. **35:** 529, 1948.

[24] Merrill, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. J. Clin. Investigation **25:** 389, 1946.

[25] Stead, E. A., Jr., Myers, J. D., Scheinberg, P., Cargill, W. H., Hickam, J. B., and Levitan, B. A.: Studies of cardiac output and of blood flow and metabolism of splanchnic area, brain, and kidney. Tr. A. Am. Physicians **63:** 241, 1950.

[26] Mokotoff, R., Ross, G., and Leiter, L.: Renal plasma flow and sodium readsorption and excretion in congestive heart failure. J. Clin. Investigation **27:** 1, 1948.

[27] Grossman, J., Weston, R. E., Halperin, J. P., and Leiter, L.: The nature of the renal circulatory changes in chronic congestive failure as reflected by renal tubular maximal functions. J. Clin. Investigation **29:** 1320, 1950.

[28] Merrill, A. J., and Cargill, W. H.: Effects of exercise on the renal plasma flow and filtration rate of normal and cardiac subjects. J. Clin. Investigation **27:** 272, 1948.

[29] Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Webster, C. A., Richards, D. W., Jr., and Cournand, A.: Some effects of digoxin on heart and circulation in man. Digoxin in chronic cor pulmonale. Circulation **1:** 161, 1950.

[30] Berger, E. Y., Galdston, M., and Horwitz, S. A.: The effect of anoxic anoxia on the human kidney. J. Clin. Investigation **28:** 648, 1949.

[31] Motley, H. L., Cournand, A., Werko, L., Himmelstein, A., and Dresdale, D.: The effect of short periods of induced anoxia upon the pulmonary arterial pressure in man. Am. J. Physiol. **150:** 315, 1947.

[32] Taussig, H. B., and Blalock, A.: Observations on the volume of the pulmonary circulation and its importance in the production of cyanosis and polycythemia. Am. Heart J. **33:** 413, 1947.

[33] Lamport, H.: Hemodynamics. In Fulton, J. F., ed.: Howell's Textbook of Physiology, ed. 16. Philadelphia, Saunders, 1949. P. 589.

[34] Pappenheimer, J. R., and Maes, J. P.: A quantitative measure of the vasomotor tone in the hind limb muscles of the dog. Am. J. Physiol. **137:** 187, 1942.

[35] Eckstein, R. W., Book, D., and Gregg, D. E.: Blood viscosity under different experimental conditions and its effect on blood flow. Am. J. Physiol. **135:** 773, 1942.

[36] Whittaker, S. R. F., and Winton, F. R.: The apparent viscosity of blood flowing in the isolated hind limb of the dog and its variation with corpuscular concentration. J. Physiol. **78:** 339, 1933.

The Cardiac Output in Chronic Cor Pulmonale

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A comparative study was made of the resting cardiac index in 12 cases of chronic cor pulmonale, in 14 normal subjects, and in 10 patients suffering from heart failure due to vascular or valvular disease. The mean cardiac index in the subjects with chronic cor pulmonale was significantly higher than in the group with other types of heart disease and was significantly lower than in the normal individuals. An explanation for the failure to observe elevation of cardiac output in some of these cases of chronic cor pulmonale is offered.

SINCE the publication of McMichael and Sharpey-Schafer,[1] cor pulmonale has been generally grouped with thyrotoxicosis, beriberi, systemic arteriovenous fistula, anemia and Paget's disease of the bone as a type of heart disease associated with a high cardiac output. During the past two years we have had the opportunity to study the hemodynamics of 15 cases of chronic cor pulmonale, and five other cases of chronic lung disease. Since we were impressed by the infrequency of high cardiac output in these 20 subjects, it was believed that a report of their findings would be of interest.

Material

The patients studied were from the medical wards of the Cincinnati General Hospital and from the Veterans Administration Hospital, Dayton, Ohio. The diagnosis of chronic cor pulmonale was made on the basis of a history of chronic lung disease, x-ray evidence of chronic lung disease (usually emphysema), and the presence of either x-ray or electrocardiographic evidence of right ventricular hypertrophy in the absence of valvular or congenital heart disease (table 1). Eight of the 15 subjects with chronic cor pulmonale had evidence of retention of carbon dioxide in the blood; all save one had resting arterial oxygen saturations below 92 per cent of capacity. Eleven of the 15 having cor pulmonale had congestive heart failure; in two the failure was irreversible. For comparative purposes, 25 patients having normal hearts and 13 patients having heart failure or a history of heart failure associated with valvular disease or vascular disease were studied.

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Method

Patients were studied in the fasting state, unsedated or having received 0.1 Gm. of Seconal. Cardiac venous catheterization was done as described by Cournand and Ranges.[2] Cardiac outputs were determined by the direct Fick principle. During the collection of expired air, mixed venous samples were obtained over a 45 second period from the proximal portion of the pulmonary artery or from the right ventricle simultaneously with blood samples from a peripheral artery. Blood was collected under oil and stored in ice water over mercury. Duplicate samples were analyzed in the Van Slyke manometric apparatus and were required to check within 0.2 volumes per cent. Two minute samples of expired air were collected in Douglas bags, measured in a Tissot spirometer and analyzed in the Haldane apparatus. Duplicate samples were required to check within 0.03 per cent. Pulmonary "capillary" pressures were measured according to the method of Hellems and co-workers.[3] Pressures were recorded by means of a five channel optical oscillograph (Hathaway).

Results

These are summarized in tables 1 and 2. Cardiac output values were considered acceptable only if the oxygen consumption fell within the range given by Dexter,[4] allowing an occasional decrease up to 8 per cent because of the age of the patient or the effect of sedation. Using this criterion, satisfactory outputs were obtained in 12 of 15 cases of chronic cor pulmonale, in 14 of 25 normals, and in 10 of 13 cases with other types of heart failure (table 1). In the normal group, the mean cardiac index was 3.3 liters per minute, with a range from 2.5 to 4.2. In the group with chronic cor pulmonale,

The mean cardiac index was 2.7 liters per minute, with a range between 1.7 and 3.8. The difference was significant at the $p < 0.02$ level (table 2). The mean cardiac index in 10 cases with other types of heart disease was 1.8 liters per minute, with a range from 1.2 to 2.9. The cardiac output in this group was significantly lower than in the normal group ($p < 0.001$) and than in the group with chronic cor pulmonale ($p < 0.01$) (table 2). If the index of only the group of nine patients having cor pulmonale with failure is compared with that of the group of 10 with "low output failure" the difference is less striking but is significant at the $p < 0.02$ level (table 2), the group with cor pulmonale and failure having a mean cardiac index of 2.6 liters. A comparison of arteriovenous oxygen differences (table 2) reveals significant differences between the group with heart failure due to hypertension or valvular disease and the normal group, $p < 0.001$, on the one hand and the group with chronic cor pulmonale on the other ($p < 0.01$). The arteriovenous oxygen differences were not significantly different in the group with chronic cor pulmonale and in the normal group.

A significant association between the cardiac index and the resting arterial oxygen saturation was found in the 12 patients with chronic cor pulmonale ($b = 0.359$; $p = < 0.01$) (table 2).

The pulmonary artery pressure was recorded in 11 of the 12 patients having chronic cor pulmonale; in the other one right ventricular pressure was recorded. There was evidence of hypertension in the lesser circuit (the mean pulmonary artery pressure was above 17 mm. Hg, or right ventricular systolic pressure above 30 mm. Hg) in all cases. Satisfactory record of the pulmonary "capillary" pressure was observed in 5 of the 12 cor pulmonale patients and in five others having chronic lung disease. The pulmonary "capillary" pressure was normal, that is, below 12 mm. Hg, in all save one. In this subject, G. An. (table 1) there was generalized irreversible heart failure. A significant negative regression was found of cardiac index on pulmonary artery mean pressure in 11 patients (table 2) having chronic cor pulmonale, but was not marked enough to be significant. Right atrial mean pressure was measured in all 12 subjects. The pressure was elevated (above 5 mm. Hg) in seven, all of whom had congestive heart failure clinically.

Five of the 15 subjects with cor pulmonale had evidence of polycythemia. All of these had congestive failure.

Discussion

The finding of high cardiac output in cor pulmonale was described by McMichael,[1] by Richards[5] and by Harvey and co-workers.[6] Harvey and co-workers postulated that the cardiac output is high in cor pulmonale due to pulmonary emphysema because of hypoxia, and that the cardiac output falls with the advent of congestive heart failure, still remaining above the normal until failure is irreversible. In their cases of cor pulmonale due to silicosis without marked hypoxia, the cardiac output was not elevated. However in diffusion fibrosis of the lung, they found elevation of the cardiac output even in the absence of hypoxia. This is unexplained, but may be due to the activity of the underlying disease.

Dexter[7] has found the cardiac output to be normal or low in a number of cases of cor pulmonale. He has found a significant negative correlation between cardiac index and pulmonary arteriolar resistance in cor pulmonale. Dexter[7] found that the cardiac output in cor pulmonale was no longer elevated when pulmonary "arteriolar" resistance rose above approximately four times normal.

In our group of 12 patients with chronic cor pulmonale, all of whom had arterial hypoxia, none had outputs above our normal range; eight had normal outputs; four had outputs below the normal. Two patients with cor pulmonale and irreversible failure had cardiac indices below 2 liters per minute.

We were unable to find evidence of negative association between cardiac index and arterial oxygen saturation; in fact a positive association was found, suggesting that the cardiac output becomes lower as the heart becomes damaged and the pulmonary artery pressure elevated by increasing hypoxia. The general finding of normal pulmonary "capillary" pressure in chronic cor pulmonale and in chronic lung disease with pulmonary hypertension is of interest. This

TABLE I.—*Hemodynamic Data of 12 Cases of Chronic Cor Pulmonale*

Case	X-Ray	ECG	Arterial Co_2 Content vol. %*	Arterial O_2 Saturation % of cap.	Mean RA Pressure mm. Hg	R V Pressure mm. Hg	P A Pressure mm. Hg Syst/Diast Mean	P C Mean Pressure mm. Hg	Cardiac Index L./min.	A V O_2 Difference cc/100 cc	Pulmonary Resistance dynes Sec. $cm.^{-5}$	Remarks
1. D. H. 61, W. M.	Pulmonary fibrosis. Emphysema. Cor pulmonale. Angiocardiogram: Right ventricular hypertrophy	Right ventricular hypertrophy	60.1 66.8	72.3	12	—	85/40 57	—	2.6	5.1	—	Reversible heart failure MBC—29%† VC—43%† Polycythemia
2. J. S. 54, W. M.	Pulmonary emphysema. Large pulmonary arteries. Cor pulmonale	Right ventricular hypertrophy	52.1	81.3	4	53/6	56/34 40	—	3.0	5.1	—	No heart failure No polycythemia
3. C. B. 57, W. M.	Pulmonary emphysema. Large right ventricle. Cor pulmonale	Right ventricular hypertrophy	65.7	51.3	17	81/16	92/50 59	—	2.1	5.4	—	Reversible heart failure Polycythemia
4. G. A. 60, C. M.	Pulmonary emphysema. Cor pulmonale	Right ventricular hypertrophy	40.3	55.2	20	—	119/54 74	19	1.8	6.3	1,331	Heart failure, irreversible Autopsy—emphysema and cor pulmonale. VC 29% No polycythemia
5. M. T. 45, W. M.	Pulmonary emphysema and fibrosis. Large pulmonary artery compatible with cor pulmonale	Right ventricular hypertrophy	46.8	85.2	10	56/12	47/28 38	—	2.5	5.3	—	Heart failure partly reversible Polycythemia VC—48% MBC—35%
6. R. W. 56, W. M.	Pulmonary emphysema. Right ventricle enlarged. Left ventricle normal	Right ventricular hypertrophy	50.7	88.4	5	53/5	—	—	3.8	3.7	—	Heart failure reversible No polycythemia
7. J. B. 53, C. M.	Pulmonary emphysema and fibrosis. Large pulmonary artery compatible with cor pulmonale	Digitalis effect	60.8	78.1	4	57/7	55/20	11	3.2	3.8	381	Heart failure reversible No polycythemia VC—36%

8. M. L. 52, W. F.	Pulmonary emphysema. Prominent pulmonary arteries consistent with cor pulmonale	Auricular hypertrophy consistent with cor pulmonale	—	89.3	1	27/4	33/13 21	6	2.4	4.8	358	No heart failure VC—63% No polycythemia
9. D. M. 46, W. M.	Cardiac enlargement. Prominent pulmonary artery. Miliary infiltrate. Cor pulmonale	Right ventricular hypertrophy	41.8	88	10	—	70/26 42	8	2.9	5.7	466	Lung biopsy—chronic interstitial pneumonitis Nodular fibrosis Early right heart failure No polycythemia VC—106% MBC—129%
10. G. A. 59, W. M.	Congenital diaphragmatic hernia. Cardiac silhouette not well visualized	Nonspecific QRS-T abnormalities. Digitalis effect	61.6	75.5	12	44/12	55/31 41	12	2.9	3.9	427	Heart failure reversible VC—32% MBC—28% Spirogram: No emphysema Polycythemia
11. L. N. 52, W. M.	Pulmonary emphysema. Cor pulmonale	Nonspecific QRS-T abnormalities. ? Digitalis effect	66.9	83.3	4.7	—	39/21 30	—	3.8	3.5	—	No heart failure VC—54% MBC—27% No polycythemia
12. H. S. 59, C. M.	Pulmonary emphysema. Prominent outflow tract, right ventricle. Cor pulmonale	Right ventricular hypertrophy	62.1	65.5	11.5	75/11	49/8	—	1.7	6.5	—	Partly reversible Heart failure VC—60% MBC—39%; Velocity index .65 No polycythemia

* Upper limit of normal—54 volumes per cent.
† % of the predicted normal.
MBC = Maximum breathing capacity.
VC = Vital capacity.
RV = Right ventricle.
RA = Right atrium.
PA = Pulmonary artery.
PC = Pulmonary "capillary."

has been observed by Dexter[7] and by Blount.[8] We have found this measurement occasionally helpful in excluding left ventricular failure. Pulmonary "arteriolar" resistance was elevated in 10 cases of chronic lung disease and chronic cor pulmonale where it was determined. Polycythemia was found in five subjects, all of whom had cor pulmonale with congestive failure. This is consistent with the observations of Baldwin and co-workers.[9]

findings and those of Blount[8] on the one hand, and those of Richards[5] and McMichael[1] on the other, is puzzling. In some cases, at least, our failure to find elevation of the cardiac output in cor pulmonale can be explained on the basis of the nearly terminal condition of the patient. Others can be explained on the basis of extremely high pulmonary arteriolar resistance, as hypothesized by Dexter.[7] Still others may have normal or low outputs associated with fibrosis

TABLE 2.—*Statistical Analysis of Hemodynamic Data in Normal Subjects, in Patients with Chronic Cor Pulmonale, and in Patients with Heart Failure due to Valvular or Vascular Disease*

Comparison	Mean Cardiac Index L./Min.	t value	p value	Mean A-V O_2 Diff.	t value	p value
1. 14 normal subjects	3.3	2.67	<0.02	4.3	1.907	<0.1
12 subjects having chronic cor pulmonale	2.7			4.9		
2. 14 normal subjects	3.3	7.38	<0.001	4.3	4.997	<0.001
10 subjects having heart failure due to valvular or vascular disease	1.8			8.0		
3. 12 subjects having chronic cor pulmonale	2.7	3.40	<0.01	4.9	3.675	<0.01
10 subjects having heart failure due to valvular or vascular disease	1.8			8.0		
4. 9 subjects having chronic cor pulmonale with failure	2.6	2.86	<0.02			
10 subjects having heart failure due to valvular or vascular disease	1.8					
5. Regression of cardiac index on arterial O_2 saturation in 12 cases chronic cor pulmonale	0.359	3.26	<0.01			
6. Regression of cardiac index on mean pulmonary artery pressure	−0.15	5.2	<0.01			

Our findings are very similar to those of Blount.[8] He, too, found elevation of the cardiac output in only an occasional case of cor pulmonale and very poor correlation between degree of hypoxia and cardiac output. Borden,[10] in his study of emphysema, did not measure cardiac output but did find no decrease in the arteriovenous oxygen difference and concluded that the cardiac output was probably not consistently elevated in emphysema.

It is not our contention that hypoxia plays no role in the genesis of chronic cor pulmonale, nor that the cardiac output is never elevated in this state, but that the cardiac output may be normal or even low. The discrepancy between our

in the lung without marked hypoxia. Even when these three groups are excluded, one still finds a few patients (for example, J. B., G. A., table 1) whose hypoxia is associated with normal cardiac output and no exceptional increase in pulmonary "arteriolar" resistance.

SUMMARY

Measurements of the pulmonary circulation were made in 12 patients suffering from chronic cor pulmonale.

The resting cardiac index was not elevated above normal limits in these patients. The mean resting cardiac index in chronic cor pul-

monale was significantly higher than in heart failure due to hypertension or valvular disease, and was significantly lower than in a normal group.

Pulmonary "capillary" mean pressure was normal in 9 of 10 cases of chronic lung disease with increased pulmonary arteriolar resistance and may be of aid in the diagnosis of cor pulmonale. Pulmonary arteriolar resistance was elevated in all 10 cases of chronic lung disease where the measurement was made.

A significant association between resting cardiac index and arterial oxygen saturation was found. A significant negative association was observed between cardiac output and pulmonary artery mean pressure.

Conclusion

It is concluded that low or normal resting cardiac index may frequently be found in chronic lung disease and cor pulmonale for one of the following reasons: absence of hypoxia; high pulmonary vascular resistance; terminal condition of the patient; or some as yet unexplained factor. The mean cardiac index in chronic lung disease and cor pulmonale was higher than in a group with heart failure or a history of heart failure due to hypertension or valvular disease. The mean cardiac index in 12 cases of chronic cor pulmonale was not higher than in normal controls, and, in fact, was significantly lower than normal.

REFERENCES

[1] McMichael, J., and Sharpey-Schafer, E. D.: The action of intravenous digoxin in man. Quart. J. Med. **13:** 123, 1944.

[2] Cournand, A., and Ranges, H. M.: Catheterization of the right auricle in man. Proc. Soc. Exper. Biol. & Med. **46:** 462, 1941.

[3] Hellems, H. K., Haynes, F. W., and Dexter, L.: Pulmonary "capillary" pressure in man. J. Applied Physiol. **2:** 24, 1949.

[4] Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Hellems, H. K.: Studies of the pulmonary circulation in man at rest. Normal variations and the interrelationships between increased pulmonary blood flow, elevated pulmonary arterial pressure, and high pulmonary "capillary" pressures. J. Clin. Investigation. **29:** 602, 1950.

[5] Richards, D. W., Jr.: Cardiac output by the catheterization technique in various clinical conditions. Federation Proc. **4:** 215, 1945.

[6] Harvey, R. M., Ferrer, M. I., Richards, D. W., and Cournand, A.: Influence of chronic pulmonary disease on the heart and circulation. Am. J. Med. **10:** 719, 1951.

[7] Dexter, L.: Pulmonary circulatory dynamics in health and disease, at rest. Bull. New England M. Center **11:** 240–246, 1949.

[8] Blount, S. G., and Anderson, L. L.: Pulmonary hemodynamics in chronic pulmonary disease. Proc. Cent. Soc. Clin. Research **24:** 16, 1951.

[9] Baldwin, E. de F., Cournand, A., and Richards, D. W.: Pulmonary insufficiency III. A study of 122 cases of chronic pulmonary emphysema. Medicine **28:** 201, 1949.

[10] Borden, C. W., Wilson, R. H., Ebert, R. V., and Wells, H. S.: Pulmonary hypertension in chronic pulmonary emphysema. Am. J. Med. **8:** 701, 1950.

Studies of Hemodynamic Changes in Humans Following Induction of Low and High Spinal Anesthesia

II. The Changes in Splanchnic Blood Flow, Oxygen Extraction and Consumption, and Splanchnic Vascular Resistance in Humans Not Undergoing Surgery

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Low and high spinal anesthesia were administered to a group of 10 waking patients without the use of vasopressor drugs. Preliminary evidence does not support the view that the induced hypotension is accompanied by significant splanchnic vasoconstriction or by homeostatic diversion of blood from the splanchnic bed to maintain the circulation in "more vital" areas.

IN PREVIOUS communications we have presented the data on the general hemodynamic and blood oxygen changes induced in humans by the administration of low and high spinal anesthesia.[11, 15] This paper deals with the changes observed in the splanchnic vascular bed in two groups of patients receiving low and high spinal anesthesia, but in whom no surgical procedure was performed. The general technic and methods have been previously described[15] and mention will be made of the technic only as it applies to the problem at hand.

Material and Methods

Ten patients, nine men and one woman, with various medical diseases, were selected at random from the medical wards. Their ages ranged from 31 to 77 years; the average age was 52.4 years. Although none had active infections or temperature elevations at the time of the study, it must be emphasized that only one of these patients was entirely free of disease, and that most of them could not be considered normal control subjects. In three there was a history of chronic alcoholism, one had a fatty liver which was thought to be healed, and another was found to have mild congestive failure, conditions which are all known to derange the normal liver function and splanchnic blood flow. For the purpose of this study, however, the selection of completely normal individuals was not deemed necessary.

After an overnight fast, 0.1 to 0.2 Gm. of pentobarbital sodium was administered and the patients were transported to the cardiovascular laboratory where the air temperature was maintained at 24 C., and the humidity was kept fairly constant. The right hepatic vein was uniformly catheterized employing a 6 to 8F Goodale birdseye catheter, introduced into a medial arm vein, and the position of the tip checked repeatedly by fluoroscopic observation. An indwelling round tip no. 16 venous needle was introduced into a lateral arm vein for delivery of the bromsulfalein drip. After a priming dose of 150 mg., the chemical was administered at a rate of 3.0 mg. per square meter of body surface per minute. Constancy of flow was insured by the use of a tunnel clamp.*

The estimated hepatic blood flow was calculated according to the method of Bradley and associates,[2] and is expressed in cubic centimeters per square meter of body surface per minute (EHBFM^2). In all instances minor variations in the peripheral concentration of bromsulfalein were adjusted by computing the estimated hepatic blood flow according to the correction factors suggested by the same authors. In this instance, total plasma volume was calculated from the tables of Gibson and Evans.[5] Cases in which the peripheral concentration of bromsulfalein (dP) exceeded .0005 mg. per minute, were discarded.

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* Harvard Instrument Co., Dover, Mass.

The calculated splanchnic oxygen consumption (CSOC) was obtained by using the formula:

$$CSOC = \frac{EHBFM^2 \times A - V\ Difference}{100},$$

wherein A-V difference represents subtraction of the oxygen content of hepatic vein blood from that of brachial arterial blood in volumes per cent, and CSOC is expressed in cc. of oxygen per minute per square meter of body surface.[13]

The brachial arterial and the hepatic venous pressure were measured respectively through a no. 19 intra-arterial needle and the hepatic catheter. Pressures were transduced via Statham strain gauges and recorded on the Brush multichannel oscillograph.

The splanchnic vascular resistance (SVR) was calculated according to the formula:

$$SVR = \frac{Mean\ arterial\ blood\ pressure}{Hepatic\ blood\ flow\ in\ cubic\ centimeters\ per\ second\ per\ square\ meter\ body\ surface},$$

and expressed as mm. Hg per cubic centimeter per second per square meter body surface.[4]

Bromsulfalein levels were determined on the Beckman DU spectrophotometer, previously calibrated to known amounts and dilutions of the dye, employing a wave length setting of 580 mv. Blood oxygen contents were determined spectrophotometrically according to the method of Hickam and Frayser.[8]

Following a stabilization period which did not exceed 60 minutes, the basal values were obtained. Low (five patients) or high (five patients) spinal anesthesia was then induced according to the previously described technic,[15] wherein the former produces a sensory anesthetic level lower than T-4 and is accompanied by diminished blood flow in the finger, and the latter leads to anesthesia above T-4 with a release of vasomotor tone in the finger. In all instances these criteria were met. Finger blood flows and volumes and toe pulse volumes were measured through oncometer air transmission, transduced via Grass and Statham strain gauges, and recorded on the Grass oscillographic plethysmograph.

All determinations were repeated 30 and 60 minutes after the induction of spinal anesthesia. Specimens for the determination of estimated hepatic blood flow were drawn in groups of three, five minutes apart, and the averages recorded. All other determinations were carried out in duplicate. *Vasopressor drugs were not employed at any time.*

As a control all determinations were carried out in an additional group of five patients over a two or three hour period. Spinal anesthesia was not administered to these patients, but all other maneuvers repeated as in the previous group.

Results

The data obtained in patients undergoing low and high spinal anesthesia are presented in tables 1 and 2, respectively.

1. Mean Brachial Arterial Pressure. This dropped an average maximal of 22.4 per cent in the "low" and 27 per cent in the "high" spinal group. These changes compare favorably with those previously reported,[15] particularly in the low spinal group. In the high spinal group the drop in blood pressure was not as pronounced as we might have expected. This was probably due to the fortuitous circumstance that the low spinal group was, on the average, 10 years older than the high spinal group, and the latter had an average resting mean pressure of 89.4 mm. Hg, as compared with the former where it was 110 mm. Hg.

2. Estimated Hepatic Blood Flow ($EHBFM^2$). There was an average maximal decrease of 24 per cent in the "low," and 33 per cent in the "high" spinal group. The estimated blood flow ($EHBFM^2$) decreased in all instances with one exception (patient A. C.) in whom an insignificant rise and fall occurred at the 30 and 60 minute periods, respectively, following low spinal anesthesia. This was the only patient with an elevated right atrial pressure (5.7 mm. Hg).

In three subjects (J. K., J. N., J. C.) the control flows exceeded the expected upper range of normal[1]; in another (P. P.) it was slightly lower.

3. Brachial Arterial-Hepatic Venous Oxygen Difference. There was an average maximal increase of 16.7 per cent in the "low" and 35.5 per cent in the "high" spinal group. Here again, patient A. C. showed a transient decrease of 1.13 volumes per cent of oxygen at the 30 minute period, and an increase of only 0.57 volumes per cent at the 60 minute period.

4. Hepatic Vein Oxygen Content. The oxygen content of hepatic venous blood decreased a maximal average of 16.2 per cent in the "low," and 30.3 per cent in the "high" spinal group. This decrease occurred in all instances except in patient C. V., in the low spinal group, who demonstrated an insignificant rise and fall at the 30 and 60 minute periods respectively. In patient A. C. there was an insignificant

TABLE 1.—*The Hemodynamic and Oxygen Changes Consequent to Low Spinal Anesthesia. Determinations Recorded in the Resting State, and 30 and 60 Minutes Following the Administration of the Anesthetic. Arterial Pressure Expressed as Systolic, Diastolic and Mean*

Patient	Age	Diagnosis	Anesthetic and Level	Brachial Arterial Pressure (mm. of Hg)			Estimated Hepatic Blood Flow (cc./M²/min.)			Brachial Arterial-Hepatic Venous Oxygen Difference (vol. %)			Hepatic Venous Oxygen Content (vol. %)			Splanchnic Oxygen Consumption (cc./M.²/min.)			Splanchnic Vascular Resistance (mm. of Hg/cc./sec./M.²)		
				Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.
J. K.	58	Cerebral thrombosis	Procaine 100 mg. T-10	149/90 117.6	135/77 105.0	127/79 99.6	1413	996	1161	5.33	7.66	7.19	8.27	5.96	6.44	75	80	83	5.0	6.3	5.1
J. N.	41	Fatty liver (healed)	Procaine 160 mg. T-8	137/80 106.0	102/63 80.4	105/69 82.2	1315	1256	945	4.40	4.57	4.99	8.23	6.87	6.73	58	57	48	4.9	3.9	4.9
A. J.	77	Hypertrophy of prostate	Procaine 100 mg. T-9	139/72 100.8	93/53 68.1	99/52 69.0	928	613	572	3.81	5.12	5.11	3.89	2.34	2.43	35	31	29	6.4	6.6	7.2
A. C.*	65	Resolved pneumonia	Procaine 100 mg. T-8	154/81 111.6	116/60 79.8	118/63 85.8	578	583	521	5.29	4.06	5.86	7.08	6.86	6.20	31	24	31	10.5	8.4	9.9
C. V.	44	Chronic alcoholism	Procaine 100 mg. T-7	136/90 114.0	117/77 94.4	115/72 90.0	662	544	510	5.10	5.28	5.36	8.13	8.16	8.00	34	29	27	10.4	10.4	10.6
Averages	57	—	—	110.0	85.5	85.3	979	798	742	4.78	5.34	5.74	7.12	6.04	5.96	46.6	44.2	43.6	7.4	7.1	7.5
Percentile change				—	−22.0	−22.4	—	−18.5	−24.2	—	+10.4	+16.7	—	−13.7	−16.2	—	−4.7	−6.8	—	−4.0	+1.3

* Patient A.C. in minimal congestive failure (right atrial mean pressure 5.7 mm. of Hg).

TABLE 2.—*The Hemodynamic and Oxygen Changes Consequent to High Spinal Anesthesia. Determinations Recorded in the Resting State, and 30 and 60 Minutes Following the Administration of the Anesthetic. Arterial Pressure Expressed as Systolic, Diastolic and Mean*

Patient	Age	Diagnosis	Anesthetic and Level	Brachial Arterial Pressure (mm. Hg)			Estimated Hepatic Blood Flow (cc./M.²/min.)			Brachial Arterial-Hepatic Venous Oxygen Difference (vol. %)			Hepatic Venous Oxygen Content (vol. %)			Splanchnic Oxygen Consumption (cc./M.²/min.)			Splanchnic Vascular Resistance (mm. of Hg/cc./sec./M.²)		
				Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.
H. W.	39	Korsakow psychosis	Procaine 160 mg. T-3	150/88 114.6	83/53 61.5	85/56 67.7	1085	910	919	5.52	8.42	7.18	10.18	6.13	7.02	60	76	66	6.4	4.1	4.4
W. R.	57	No disease	Procaine 160 mg. T-2	94/65 80.5	72/44 60.0	86/55 73.8	744	511	656	4.80	7.22	6.10	10.54	7.43	8.60	36	37	40	6.5	7.1	6.8
J. C.	31	Peptic ulcer	Procaine 125 mg. T-2	107/68 88.8	84/55 72.6	79/54 67.8	1282	934	647	4.59	6.41	7.23	13.58	11.17	10.34	59	60	47	4.1	4.7	6.3
P. P.	45	Alcoholic neuropathy	Procaine 200 mg. T-2	105/61 81.0	76/54 63.6	59/42 46.8	493	303	295	5.10	7.50	8.63	11.49	9.18	7.98	25	23	25	9.9	12.5	9.5
C. P.	59	Psychoneurosis	Procaine 175 mg. T-2	98/66 82.2	67/50 58.4	66/50 60.6	810	504	432	5.46	9.98	9.22	9.48	4.60	5.52	44	50	40	6.1	7.0	8.4
Averages	46	—	—	89.4	63.2	63.3	883	632	590	5.09	7.90	7.67	11.05	7.70	7.80	45	49	44	6.6	7.1	7.1
Percentile change				—	−27.0	−27.0	—	−28.4	−33.1	—	+35.5	+33.6	—	−30.3	−28.6	—	+8.8	−2.2	—	+7.0	+7.0

drop at the 30 minute period, as would be expected from the values already noted in his instance.

The data so far presented are significant when compared with the results in the five control patients. Because of the individual variability in the data, the changes in the estimated hepatic blood flow and in the arteriovenous oxygen difference at the 30 minute period in the low spinal group are not statistically significant. The general trend of change here, as in the remainder of the study, however, is in a downward and upward direction respectively.

5. Calculated Splanchnic Oxygen Consumption (CSOC). In the "low" spinal group there were average decreases of 4.7 and 6.8 per cent at the 30 and 60 minute periods respectively. In the "high" spinal group there was an average rise of 8.8 per cent and a fall of 2.2 per cent at these same periods.

In four subjects (J. K., J. N., H. W., J. C.) the calculated splanchnic oxygen consumption (CSOC) exceeded the known upper range of normal (a reflection of the high estimated hepatic blood flows.)

6. Splanchnic Vascular Resistance (SVR). This showed no significant change in the patients undergoing "low" spinal anesthesia, and a rise of only 7 per cent in the patients undergoing "high" spinal anesthesia. When compared with the average decreases of 8.5 and 11 per cent in the control group, these changes are not sufficiently clear cut to permit conclusive evaluation.

7. Hepatic Vein Mean Pressure. The extreme variability which occurred in individual patients, and the lack of data in regard to extravascular pressures, preclude assessment of these values.

Discussion

As has been previously shown[11, 15] the higher the level of anesthesia, the greater is the drop in the brachial arterial pressure and in the cardiac output. A close but not strict correlation was found in the decrease of the arterial pressure and the cardiac output, and the increasing level of anesthesia.

The splanchnic bed participates in the decreased rate of circulating blood during spinal anesthesia. The estimated hepatic blood flow decreases, the hepatic venous oxygen content decreases, and the brachial arterial-hepatic venous oxygen difference increases. These changes are intensified as higher cord levels are anesthetized. A close but not absolute relation may be noted between these changes and the level of anesthesia (fig. 1). The increased extraction of oxygen from the splanchnic blood is readily explained by the probable existence of a more prolonged contact between blood circulating in this bed and cells available for extraction. The cause of the retardation of flow which has been shown to exist is more difficult to explain. It is of considerable interest that Habif and his associates[6] have shown that cyclopropane, ether and Thiopental anesthesias cause similar changes in flow in the absence of a decrease in the peripheral arterial pressure, and their findings indicate that renal and splanchnic vasoconstriction causes an increased

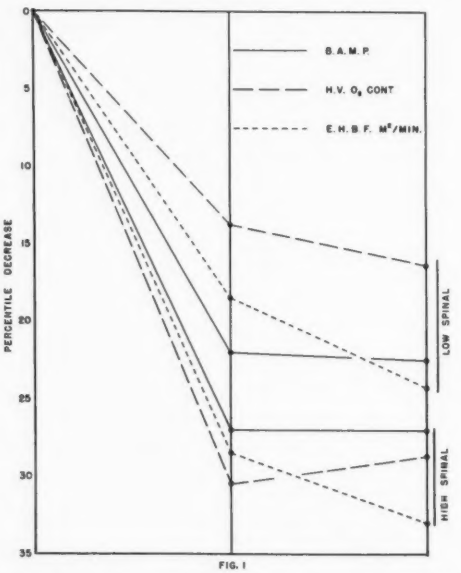

FIG. 1. Gross correlation among the mean brachial arterial pressure, the hepatic venous oxygen content and the estimated hepatic blood flow, shown as percentile changes, at the 30 and 60 minute periods following induction of the anesthetic (averages of five cases in the "low" and five cases in the "high" spinal groups).

resistance in the vascular beds of these organs. This would support the belief that the renal and splanchnic vascular beds sacrifice their recipient blood as part of a homeostatic mechanism designed to maintain an elevation of the arterial pressure and the diversion of blood to more "vital" areas, in the same fashion as is stated to occur in oligemic shock, congestive heart failure and periods of violent exercise.[3, 10, 12]

It is not likely that this same phenomenon is operative during spinal anesthesia, at least in regard to the splanchnic bed, at levels of blood pressure decreases in the order of those herein presented. Both in "high" and in "low" spinal anesthesia the changes in splanchnic vascular resistance are not significant and are variable from patient to patient. The slight average increase in splanchnic resistance noted only in "high" spinal anesthesia is so slight as to defy any definite conclusion.

Added evidence against participation of the splanchnic bed in such a diversionary homeostasis during spinal anesthesia is afforded by a combined study in patient W. R. (table 3). By placing cardiac catheters into the pulmonary artery and the hepatic vein, simultaneous determinations of the cardiac output, the estimated hepatic blood flow and blood oxygen contents could be obtained. Reduction of the saline catheter drip systems to 10 drops a minute and doubling of the amount of heparin employed prevented the development of hypervolemia. It will be noted that the percentile contribution of the splanchnic flow to the total cardiac output remained remarkably constant. Further work to test these findings is in progress. The very close relation of changes between the cardiac index, the brachial arterial pressure, the estimated hepatic blood flow and the oxygen contents of the hepatic venous and the pulmonary arterial bloods in this patient is readily seen. Papper and his associates[14] have likewise found a relation between the estimated hepatic blood flow and the arterial pressure in patients undergoing surgery under high spinal anesthesia.

As is the case in general anesthesia,[6] spinal anesthesia is followed by little or no alteration in splanchnic oxygen consumption. Contrary to the mechanism which is said to be involved in general anesthesia, however, the decrease in estimated hepatic blood flow does not appear to be due to splanchnic vasoconstriction, but to a reduced rate of inflow of blood into the splanchnic bed.

Investigation now in progress indicates that "high" spinal anesthesia leads to a marked reduction of the coronary blood flow.[7] The marked reduction and, in some instances, total temporary abolition of urinary flow during "high" spinal anesthesia, is indirect evidence that the renal bed likewise is subject to a putative decrease in blood flow. Cerebral blood flow does not appear to show any appreciable change in normotensive subjects.[9] Only in the skin, and probably in the muscles, has an increase in blood flow been demonstrated, associated with an increase in femoral vein oxygen content and a decrease in brachial arterial-femoral venous oxygen difference.[16]

There is a proportionately greater increase in the brachial arterial-hepatic venous than in the brachial arterial-pulmonary arterial oxygen difference. The conclusion is tentatively

TABLE 3.—*The Data in Patient W. R. Catheters Introduced in Hepatic Vein and Pulmonary Artery with Simultaneous Determinations of Cardiac Output and Hepatic Flow*

	Control	30 min.	60 min.
Heart rate	68	67	62
Brachial arterial pressure	94/65	74.5/46	86/55.5
Brachial arterial mean pressure	80.4	60.0	73.8
Brachial arterial oxygen content	15.34	14.65	14.70
Pulmonary arterial oxygen content	11.10	9.14	10.15
Brach. art.–pulm. art. oxygen difference	4.24	5.51	4.55
Brach. art.–hep. ven. oxygen difference	4.80	7.22	6.10
Cardiac index	2.80	2.02	2.70
EHBFM[2]	0.74	0.51	0.65
EHBFM[2] % contribution to total cardiac index	26	25	24

* Pressures in mm. of Hg, oxygen contents and differences in volumes per cent, cardiac index and EHBFM[2] in liters per minute.

reached that the increase in arteriovenous oxygen difference between arterial and mixed venous blood which follows spinal anesthesia is in part due to an increased extraction of oxygen in the splanchnic bed preponderant over the total changes which occur in the remaining vascular beds of the body. The important role of the renal vasculature, normally the recipient of 25 per cent of the resting cardiac output, has not as yet been assessed.

Summary and Conclusions

1. The brachial arterial pressure, the hepatic venous blood flow, the oxygen contents of hepatic, pulmonary (one case) and brachial arterial bloods, the splanchnic oxygen consumption and the splanchnic vascular resistance were determined in 10 patients with various medical diseases, to whom a spinal anesthetic was administered. The level of anesthesia was "low" in five patients and "high" in five patients. Determinations were made basally, 30 and 60 minutes following the administration of the anesthetic. Surgery was not performed in these patients. Vasoconstrictor drugs were not employed despite the development of hypotension. Control observations were made in five patients not receiving a spinal anesthetic.

2. Spinal anesthesia produces the following alterations: (a) a decrease in the peripheral arterial pressure; (b) a decrease in the estimated hepatic blood flow; (c) an increase in the brachial arterial–hepatic venous oxygen difference, and a decrease in the hepatic venous oxygen content.

3. Neither "low" nor "high" spinal anesthesia produce significant changes in splanchnic oxygen consumption and resistance. The absence of grossly calculable splanchnic vasoconstriction, coupled with preliminary observations that the percentile contribution of the hepatic blood flow to the total cardiac output remains unchanged during spinal anesthesia productive of hypotension of the order observed, indicates that blood is not diverted from the splanchnic bed during such hypotension as part of a homeostatic mechanism designed to maintain circulation in "vital" areas.

4. Spinal anesthesia has previously been shown to increase the brachial arterial-pulmonary arterial oxygen difference. Partial evidence is presented which indicates that a relative increase in oxygen extraction in the splanchnic bed, predominating over the extraction changes occurring in the remaining beds, is in part responsible for this change.

5. The data corroborate previous tentative conclusions which correlate the degree of hemodynamic change consequent to spinal anesthesia to the dermatomic level of the anesthetic.

References

[1] Bradley, S. E.: Variations in hepatic blood flow in man during health and disease. New England J. Med. **240:** 456, 1949.

[2] —, Ingelfinger, F. J., Bradley, G. P., and Curry, J. J.: The estimation of hepatic blood flow in man. J. Clin. Investigation **24:** 890, 1945.

[3] Chapman, C. B., Henschel, A., Minckler, J., Forsgren, A., and Keys, A.: The effect of exercise on renal plasma flow in normal male subjects. J. Clin. Investigation **27:** 639, 1948.

[4] Culbertson, J. W., Wilkins, R. W., Ingelfinger, F. J., and Bradley, S. E.: The effect of the upright posture upon hepatic blood flow in normotensive and hypertensive subjects. J. Clin. Investigation **30:** 305, 1951.

[5] Gibson, J. G., and Evans, W. A., Jr.: Clinical studies of the blood volume. II. The relation of the plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex in ninety normal humans. J. Clin. Investigation **16:** 317, 1937.

[6] Habif, D. V., Papper, E. M., Fitzpatrick, H. F., Lowrance, P., McC. Smythe, C., and Bradley, S. E.: The renal and hepatic blood flow, glomerular filtration rate, and urinary output of electrolytes during cyclopropane, ether and Thiopental anesthesia, operation, and the immediate postoperative period. Surgery **30:** 241, 1951.

[7] Hackel, D. H.: Unpublished Observations.

[8] Hickam, J. B., and Frayser, R.: Spectrophotometric determination of blood oxygen. J. Biol. Chem. **180:** 457, 1949.

[9] Kleinerman, J., Sancetta, S. M., Lynn, R. B., Stahl, R., and Hackel, D. B.: Studies of hemodynamic changes in human beings following induction of high spinal anesthesia. III. The effects on cerebral blood flow, cerebral oxygen and glucose metabolism. Proc. Central Soc. Clin. Res. **25:** 1952 (Abstract). To be published.

[10] Lauson, H. D., Bradley, S. E., and Cournand, A.: The renal circulation in shock, J. Clin. Investigation **23:** 381, 1944.

[11] Lynn, R. B., Sancetta, S. M., Simeone, F. A., and Scott, R. W.: Observations on the circulation in high spinal anesthesia. Surgery **32:** 195, 1952.

[12] Merrill, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "Forward Failure" as the primary cause of edema. J. Clin. Investigation **25:** 389, 1946.

[13] Myers, J. D.: The hepatic blood flow and splanchnic oxygen consumption in man. Their estimation from urea production or bromsulfalein extraction during catheterization of the hepatic veins. J. Clin. Investigation **26:** 1130, 1947.

[14] Papper, E. M., Habif, D. V., and Bradley, S. E.: Studies of renal and hepatic function in normal man during thiopental, cyclopropane and high spinal anesthesia. J. Clin. Investigation **29:** 838, 1950 (Abstract).

[15] Sancetta, S. M., Lynn, R. B., Simeone, F. A., and Scott, R. W.: Studies of hemodynamic changes in humans following induction of low and high spinal anesthesia. I. General considerations of the problem. The changes in cardiac output, brachial arterial pressure, peripheral and pulmonary oxygen contents, and peripheral blood flows induced by spinal anesthesia in humans not undergoing surgery. Circulation **6:** 559, 1952.

[16] Unpublished observations.

Studies on Acute and Chronic Toxicity of Tetraethyl Ammonium Ion (Etamon)

Methods of Reviving Dogs after a Lethal Dose

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Studies were done using dogs to determine: (1) the ED_{50}* of Etamon when given as an infusion over 30 minutes; (2) the possibility of an accumulative toxicity when Etamon is given in multiple small doses over long periods of time; and (3) the effect of various measures in preventing death after the administration of a lethal dose (LD_{100}*) of Etamon. The ED_{50} of Etamon given as an infusion was found to be nearly twice that of Etamon given as a fast injection intravenously. There seemed to be an accumulative toxic effect following the use of Etamon in multiple small doses over a long period of time as evidenced by the difference between the ED_{50} of those receiving a single large infusion and those receiving multiple small infusions. Intermittent controlled positive pressure respirations were found to be effective in preventing death after the infusion of a lethal dose of Etamon.

IN a recent paper by McLemore, Green, and Lide[1] the ill effects of tetraethyl ammonium ion (Etamon) were reviewed. Two deaths following the infusion of Etamon were reported. One was attributed to myocardial infarction, and the other was attributed to respiratory paralysis. The results of an experiment in which four dogs were given progressively increasing doses of Etamon at the rate of four infusions daily were also reported. These dogs ultimately died of a respiratory paralysis at a mean dose of 35 mg. per kilogram.

In the present paper we report the results of further work which has been done on a larger group of dogs in an effort to determine: (a) the ED_{50} (MLD_{50}*) of Etamon when given as an infusion over 30 minutes, (b) the possibility of an accumulative effect following repeated Etamon infusions, (c) the efficacy of Prostigmin methyl sulfate (neostigmine), oxygen, tracheal cannulation, manual artificial respiration, nikethamide (Coramine), caffeine and sodium benzoate, and intermittent controlled positive pressure respiration, alone or in combination, in overcoming the respiratory paralysis and preventing death after the infusion of a lethal dose of Etamon.

The single dose studies (to determine the ED_{50}) were done in order to check the safety of diagnostic studies in which only single infusions are required. Multiple dose studies were done because of the fact that one of the patients reported by McLemore and coworkers, was on low multiple doses and death was attributed to respiratory paralysis which was thought to have resulted from a toxic accumulation.

The work on ED_{50} and accumulative toxicity will be presented in part I; the work on methods of preventing death will be presented in part II.

I. DETERMINATION OF ED_{50}; STUDIES ON ACCUMULATIVE TOXICITY

A. Determination of ED_{50} for Single Infusions of Etamon

Methods. The methods in the four groups of animals used to make this determination were

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* LD_{100} = Dose which will cause death in 100 per cent of animals.

MLD_{50} = Minimal dose at which 50 per cent of animals will die.

ED_{50} = Dose, as estimated by method of Litchfield and Wilcoxon,[2] at which 50 per cent of animals are expected to die.

the same. The dose of Etamon was given in 100 ml. of saline over a period of 30 minutes and the dogs were allowed to be up with no restraints. No anesthesia was used. The general health of the animals was good and the range in weight was from 5.0 Kg. to 12.0 Kg. Those dogs that survived the given dose were not used again for any other part of the experiment. The doses for groups 1 to 4, respectively, were 50, 60, 70 and 80 mg. per kilogram.

TABLE 1.—*ED_{50} Following Single Infusions*

Group No.	No. Dogs in group	TEA dose (mg./Kg.)	No. dogs survived	No. dogs that died
1	6	50	5	1
2	7	60	3	4
3	6	70	3	3
4	6	80	0	6

ED_{50}, 63.5 mg./Kg.
Confidence Limits, 55.7–72.4 mg./Kg.

TABLE 2.—*(Group 5). ED_{50} Following Weekly Infusions*

Dog No.	Total No. infusions	Dose at Death (mg./Kg.)	Av. Weight of dog (Kg.)
1	2	45	7.4
2	5	60	3.8
3	5	60	5.2
4	5	60	6.9
5	9	80	9.8
6	10	85	4.8
Mean	6.0	65.0	6.3
S.D.	2.7	13.6	1.9

ED_{50}, 62.0 mg./Kg.*
Confidence Limits, 69.0–55.7 mg./Kg.
* See footnote to table 4.

Results. Observation of the dog following infusion of the drug revealed the following to be the most marked symptoms: generalized muscular weakness, muscular incoordination, tachycardia, dyspnea (those that died showed dyspnea followed by apnea), excitement, and cyanosis. In those which lived, a normal equilibrium was established after about a 12-hour period. The statistical results for this group are shown in table 1. In determining the ED_{50} the method described by Litchfield and Wilcoxon[2] in their paper on evaluating dose effect experiments was used.

B. Studies on Accumulative Toxicity of Etamon

Methods. Three groups of dogs were used in this determination. The method of infusion was the same as that described for the previously discussed groups except for the fact that these dogs received multiple doses at varying intervals of time. In group 5 each dog received a weekly dose, the initial dose being 40 mg. per kilogram, with increments of

TABLE 3.—*(Group 6). ED_{50} Following Biweekly Infusions*

Dog No.	Total No. Infusions	Dose at Death (mg./Kg.)	Av. Weight of Dog (Kg.)
1	7	55	7.0
2	9	60	9.7
3	11	65	6.1
4	11	65	8.5
5	13	70	6.5
6	15	75	6.6
Mean	11.0	65.0	7.4
S.D.	2.6	6.5	1.3

ED_{50}, 62.0 mg./Kg.*
Confidence Limits, 65.4–58.7 mg./Kg.
* See footnote to table 4.

TABLE 4.—*(Group 7). ED_{50} Following Infusions Four Times Daily*

Dog No.	Total No. Infusions	Dose at Death (mg./Kg.)	Av. Weight of Dog (Kg.)
1	24	30	7.3
2	32	35	6.6
3	31	35	7.0
4	40	40	7.4
Mean	31.0	35.0	7.1
S.D.	5.7	3.5	0.1

ED_{50}, 32.5 mg./Kg.*
Confidence Limits, 36.3–29.1 mg./Kg.
* The method described by Litchfield and Wilcoxon to determine the ED_{50} for single dose studies was modified as follows for the determination of the ED_{50} in these multiple dose studies: It was assumed that if dog 1 in group 5 died at a dose of 45 mg. per kilogram, then he would have died also at 85 mg. per kilogram, the dose at which dog 6 died. This assumption, plus the fact that the initial dose in all the dogs was 40 mg. per kilogram, permitted us to derive a table in which there are six animals for each dose which caused death. The table presented is for group 5 as an example.

5 mg. per kilogram each week until death. In group 6 each dog received biweekly doses, the initial dose being 40 mg. per kilogram, with increments of 5 mg. per kilogram each week until death. In group 7 each dog received four doses daily, the initial dose being 20 mg. per kilogram, with increments of 5 mg. per kilogram every two days until death. The general health of the dogs was good. The weight range was from 3.8 to 9.8 Kg. As before, no anesthesia was used and the dogs were allowed up immediately after the infusion. The results for the groups are tabulated in tables 2, 3, and 4, respectively.

Discussion

The determination of the ED_{50} for single infusions requires no discussion or comment except to note that the ED_{50} of 63.5 mg. per kilogram is nearly twice that mentioned by Krantz and Carr, 36 mg. per kilogram, for single nondiluted injections given rapidly.

TABLE 5.—*Group 5*

Dose (mg./Kg.)	Number Alive	Number Dead
40	6	0
45	5	1
50	5	1
55	5	1
60	2	4
65	2	4
70	2	4
75	2	4
80	1	5
85	0	6

ED_{50}, 62.0 mg./Kg.*
Confidence Limits, 69.0–55.7 mg./Kg.
* See footnote with table 4.

In the studies on accumulative toxicity it should be noted that the ED_{50} for groups 5 and 6 are identical, except for some slight variation in the confidence limits. The same is true for the mean dose at death. In contrast to these two groups is the ED_{50} of 32.5 mg. per kilogram in group 7. This finding indicates that tetraethylammonium does have an accumulative toxicity when given in multiple doses at short intervals.

In comparing the ED_{50} of groups 5 and 6 with that of groups 1 to 4 it is striking to note that the difference is negligible (1.5 mg. per kilogram). On the basis of this observation one may conclude that death in groups 5 and 6 was probably the result of the last single lethal dose and probably would have occurred at that particular dose, even had there been no previous infusions.

In comparing the time intervals between infusions in groups 6 and 7 one may conclude that, if sufficient time has elapsed for the total excretion of the drug and recovery from any adverse metabolic effects, no evidence of accumulative toxicity will be noted. The results in these two groups indicate that two to three days are ample for excretion of the drug and recovery; but that the drug, if given in several injections per day, will become toxic due to an accumulative effect.

II. Studies in Methods of Preventing Death After the Administration of a Lethal Dose of Etamon

Method. A total of 24 dogs was used in this study. The animals were in good general health. The procedures were done under a local anesthesia, 1 per cent Novocain. The femoral artery and vein were exposed and cannulated. Infusions were given via the venous cannula. The femoral pulse (blood pressure), electrocardiogram, and respiratory excursions were recorded on a polyviso amplifier. The Etamon in each instance was given in the same manner as that described in part I, that is, in 100 ml. of saline over a period of 30 minutes. Continuous recordings were made during each experiment in order that all changes could be recorded and noted. There was an approximately equal distribution in the number of each sex used. The weight range was from 4.5 Kg. to 13.5 Kg. The dosage given each dog is tabulated in table 6.

The methods and drugs which were tried as measures to save the animals after the administration of a lethal dose of Etamon were as follows: (a) Prostigmin methyl sulfate, (b) tracheal cannulation, (c) oxygen, (d) Coramine, (e) caffeine and sodium benzoate, (f) calcium gluconate, (g) manual artificial respiration with external cardiac massage, and (h)

intermittent controlled positive pressure respirations. Reasons for the use of these procedures are discussed later.

These various measures were tried alone and in combination. The Prostigmin was given by drip over periods ranging from 5 minutes to 30 minutes and in doses ranging from 0.5 mg. to 2.0 mg. The dose of Coramine was 1.5 ml. of a 25 per cent aqueous solution. The dose of caffeine and sodium benzoate was 0.5 Gm. in 1.0 ml. These latter two drugs were given as an intravenous injection and no more than one dose was administered to any one animal. Calcium gluconate, 20 ml. of a 10 per cent aqueous solution, was given to one animal.

In order that there should be no question concerning whether or not the animals would have survived without some life-saving method being instituted, 17 animals were allowed to become extremely cyanotic, and the blood pressure was allowed to fall to very low levels (0 to 25 mm. Hg systolic). Early there was tachycardia, then bradycardia; the latter was often accompanied by a partial or complete heart block, premature ventricular systoles, and, infrequently, an idioventricular rhythm or ventricular tachycardia. The prodromal signs were: (a) fibrillary movements of the skeletal musculature, (b) dyspnea with periods of apnea, (c) extreme restlessness, and (d) narrowing of the pulse pressure followed by an increase in the systolic pressure with a concomitant increase in the pulse pressure. (See figures 1 and 2.) The latter changes accompanied the anoxia due to the respiratory failure and preceded the circulatory failure. Death in all instances was due to the respiratory failure (fig. 1). In addition to the 17 animals mentioned above Prostigmin was given to seven animals before overt signs of respiratory paralysis were present. These will be described more fully later.

As soon as a toxic state was observed the particular method to be investigated was instituted immediately. If no response was observed, another method was then instituted. Frequently, the animal was in such a state of collapse that no method was effective. In such cases external cardiac massage was initiated and continued until such time as the animal was able to maintain its arterial pressure with no aid other than that furnished by the method under investigation. It was felt that this did not offer any variables in determining the efficacy of the other methods, since our interest was in long term results and not in the short transient recovery that was sometimes achieved with the cardiac massage.

The machine used for giving intermittent controlled positive pressure respirations was a windshield wiper converted so that the part normally used for the blade was fitted with a stopcock which rotated 90 degrees, thus letting the air through intermittently. The air was piped in under pressure from an outside source. A tracheal cannula was used to conduct the air. The space around the cannula was of sufficient size to permit full expiration after the forced inspiration. The effectiveness of the cannula used in such a manner can probably be ascribed to a decrease in the dead space as a result of inserting the cannula far down in the trachea.

From previous experience (see part I) it was thought that a lethal dose (LD_{100}) of Etamon given as a single infusion was probably around 70 mg. per kilogram. Therefore, several animals were given that dose. Two animals survived this dose and it was thought best to raise the dose level so that a consistently toxic state could be achieved. After some experimentation it was found that 80 mg. per kilogram was a lethal dose in most of the animals. In those animals that survived this dose an additional 200 mg. dose was given.

Results. The adults are tabulated in table 6, which shows the dose of Etamon received, the methods used in an effort to prevent death, and the results of such efforts. Except in seven animals in which Prostigmin was administered before overt signs of respiratory paralysis were present, no aid was given unless a severely toxic state was achieved.

Discussion. Work with prostigmine was stimulated by a report, by Reardon and co-workers,[3] that this drug would reverse the changes observed as a result of Etamon infusion. Our experience with the drug does not bear this out, as can be seen from the resume of the 12 dogs to which the drug was given (fig. 1).

TABLE 6.—*Tabulation of the Effect of Various Procedures Tried in Reviving Dogs After the Administration of a Lethal Dose of Etamon*

Dog No.	Dose of TEA	Method(s) Used	Results
	(*mg./Kg.*)		
1, 2	70		Survived this dose without any method being used
3	70	Tracheal cannulation	Not effective
		Manual artificial respiration with external cardiac massage	Effective as long as continued
		Oxygen via tracheal cannula	Not effective without manual artificial respiration.
		Caffeine and sodium benzoate (0.5 Gm. in 1.0 ml.)	Not effective; animal did not survive
4	(1) 85	Oxygen via tracheal cannula	Not effective without manual artificial respiration
		Manual artificial respirations	Dog resumed respiratory function and arterial pressure stabilized in one hour
	(2) 45	Oxygen via tracheal cannula	Same as above
		Manual artificial respirations	Dog resumed respiratory function and lived 5 days in a moribund condition. Sacrificed
5	80	Oxygen via tracheal cannula	Not effective without manual artificial respirations
		Intermittent controlled positive pressure respirations	Blood pressure rose and stabilized. Stopped after 30 minutes. Dog immediately showed signs of collapse.
		Manual artificial respirations	Not effective due to extremely poor condition of the animal
		Caffeine and sodium benzoate (0.5 Gm. in 1 ml.)	Dog did not survive
6	80	Calcium gluconate (20 ml. of 10% aqueous solution)	Dog did not survive
7	70	0.5 mg. Prostigmin (infusion)	Not effective
		Tracheal cannulation	Not effective
		Manual artificial respirations, with external cardiac massage	Effective as long as continued
		Coramine, 1.5 ml. of a 25% aqueous solution	Not effective. Dog did not survive
8	70	0.5 mg. Prostigmin (infusion)	Not effective
		Tracheal cannulation	Not effective
		Manual artificial respirations with external cardiac massage	Effective as long as continued
		Oxygen via tracheal cannula	Not effective without manual artificial respirations
			Dog did not survive
9	80	0.5 mg. Prostigmin (infusion)	Not effective
		0.5 mg. Prostigmin (injection)	Not effective
		Tracheal cannulation	Not effective
		Manual artificial respiration with external cardiac massage	Effective as long as continued
			Dog did not survive

TABLE 6—*Concluded*

Dog No.	Dose of TEA	Method(s) Used	Results
	(mg./Kg.)		
10	(1) 80		Survived this dose
	(2) 60	Tracheal cannulation; this was followed immediately with 0.5 mg. Prostigmin	Dog recovered complete respiratory function in 1 hour. There is some doubt as to whether an absolute paralysis ever developed
11–17		These 7 dogs were all given 80 mg./Kg. of Etamon over 30 minutes, followed immediately, before any signs of respiratory paralysis had developed, by an infusion of Prostigmin. Four animals received 1.0 mg., and three others received 2.0 mg., 0.7 mg., and 0.5 mg., respectively. Of this group 2 lived, one having received 1.0 mg. and one having received 0.5 mg. It cannot be said with certainty that these animals would not have survived had the Prostigmin not been given, since other animals had survived the 80 mg./Kg. dose. (See figure 1.)	
18–24		All of the animals in this group received 80 mg./Kg., except for 3 which required extra doses of 200 mg. before they developed a respiratory paralysis. As soon as the paralysis developed the tracheal cannula was inserted and intermittent controlled positive pressure respirations were begun. The blood pressure in every instance returned to normal levels within 3–5 mins. and the animals regained their respiratory function in an average time of 1½ hrs. In 5 animals which received 150 ml. of physiologic saline the recovery time was somewhat shorter, being about 1 hour. One animal was given a total dose of 240 mg./Kg. in three doses without the controlled respirations being stopped. In this case full respiratory function was regained in 4 hours after the initial dose. (See figure 2.)	

Although two of the animals did live in which the drug was given before there were any signs of respiratory paralysis, it cannot be stated with certainty that they would not have lived without the drug, since four other animals did survive the 80 mg. per kilogram dose without aid. In the 18 dogs which received an initial dose of 80 mg. per kilogram, 17 per cent survived without any aid being given; while in the group of 12 dogs receiving Prostigmin there was a 16 per cent survival. This in itself would indicate that Prostigmin was probably not the effective agent in the two animals that lived after having received the drug. In the other animal that lived after having received the drug it is doubtful, after reviewing the record, that the animal did acquire a complete paralysis before the drug was given.

The insertion of the tracheal cannula was tried when it was noted that the dogs exhibited signs of laryngeal spasm or paralysis, for example, stridor. It was thought that a measure which would open this part of the respiratory tree would lessen the amount of respiratory difficulty. Oxygen was added to this procedure since it was thought that there was a decrease in the tidal volume. The procedure, as can be seen from table 5, was not effective, since the respiratory difficulty was chiefly central in character.

Coramine and caffeine and sodium benzoate, two central respiratory stimulants, were of no value in overcoming the paralysis produced by Etamon. The calcium gluconate was used after it was observed that fibrillary movements of the muscles were present before the absolute paralysis set in, these fibrillations probably being due to a repetitive discharge at the nerve endings. The calcium did not cause a cessation of this phenomenon.

It was observed in many of the animals in which other methods had been used that manual artificial respiration was successful in bringing about a temporary recovery, failure again ensuing if the artificial respiration was not continued. If there was a circulatory collapse after the measure was stopped, recovery again could be achieved if the artificial respiration was reinstituted. Two dogs were revived in this manner 14 and 16 times before

death finally ensued, probably as a result of pulmonary edema or trauma to the heart associated with manual artificial respirations in the dog. One dog fully recovered his respiratory function following the use of this procedure; yet, he was in a moribund state for the remainder of the five days he lived before being sacrificed. It was felt by the observers that the anoxia incident to the periods of apnea when the artificial respiration was omitted probably caused irreversible damage to the central nervous system.

The institution of manual artificial respiration in a human subject in whom there is a respiratory paralysis following Etamon infusion would probably be successful, but the difficulty in moving large volumes of air and the strenousness of the procedure, plus the fact that it is effective for only as long as it is continued, leaves much to be desired. Were it possible to continue the method for a period of time sufficient to permit excretion of the drug and the recovery of respiratory function, then probably it would be in the same order of effectiveness as the intermittent controlled positive pressure respirations discussed in the following paragraphs.

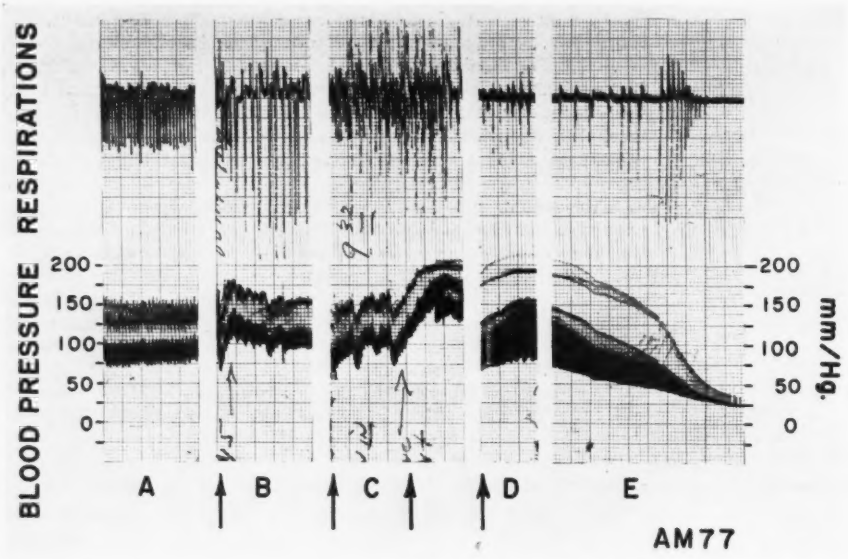

FIG. 1. Records of respirations and arterial pressure in a dog given a toxic dose of Etamon and receiving only Prostigmin in an effort to prevent respiratory and vascular collapse. Upper curve shows respirations, recorded with a pneumograph, the downward deflection illustrating inspirations. Lower record shows arterial pressure, recorded by cannula in the femoral artery, connected to a Statham strain gauge. Figures give pressure in mm. Hg. *A*. Controls made two minutes before *B*. Arrow at *B* indicates start of Etamon infusion at time 0 minutes. First arrow at *C* indicates completion of Etamon infusion at 30 minutes. Total dose given, 80 mg. per kilogram. Second arrow in *C* at 31 minutes indicates beginning of Prostigmine infusion. Arrow at *D* indicates completion of Prostigmine infusion at 46 minutes. Total dose given, 1.0 mg. Terminal changes with death at 50 minutes are shown in *E*. Time: 5 mm. (distance between two heavy lines) = 20 seconds. Dog weight: 8.5 Kg. Male.

Following the observation that manual artificial respirations were effective for as long as they were continued in overcoming the respiratory paralytic effect of Etamon, intermittent controlled positive pressure respirations were used in the hope that a method which could achieve a successful gaseous exchange in the lungs and be operated easily over long periods of time would give the animal suf-

ficient time to excrete the drug and regain his respiratory function. The initial two dogs which were given intermittent controlled positive pressure respirations died. Death in one ensued when a compressed air conducting tube ruptured. Death ensued in the second dog when the machine was stopped after one and one half hours in order that we could check for any signs of regained respiratory function. Vascular collapse ensued immediately and we were not able to revive the animal.

Seven other dogs survived after being given intermittent controlled positive pressure respirations for periods of time ranging from 30 minutes to four hours (fig. 2). The average length of time necessary to recover their respiratory function for those dogs that did not receive 150 ml. of physiologic saline was one and one half hours. For those that received the saline, the average time required for recovery was about one hour. One animal received a total dose of 240 mg. per kilogram of the drug, which was given without the intermittent controlled positive pressure respirations being stopped. This dog regained his respiratory function within four hours and is an excellent example of the efficacy of this method.

In the beginning it was thought that there might be some inhibition of bladder function following the autonomic ganglionic blockade by Etamon, but it was noted that, in almost every dog, there was neither difficulty in urination nor any obvious decrease in the quantity of the urine. As has been noted, those dogs that were well hydrated regained their respiratory function in a shorter period of time than did those to whom no fluid was given.

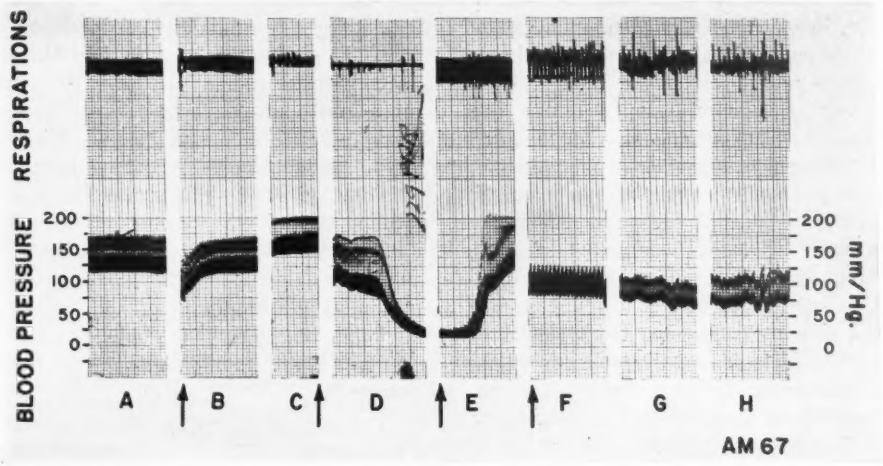

FIG. 2. Similar to figure 1 but shows effects of intermittent controlled positive pressure respirations on the respiratory and vascular failure induced by a toxic dose of Etamon. *A*. Controls made two minutes before *B*. Arrows at *B* and *C* indicate the beginning and completion of the Etamon infusion at times 0 and 30 minutes, respectively. Total dose, 80 mg. per kilogram. *D* shows respiratory and vascular collapse occurring at 57 minutes. Arrow at *E* indicates the institution of intermittent controlled positive pressure respirations at 58 minutes. Arrow at *F* indicates cessation of intermittent controlled positive pressure respirations at 73 minutes. *G* and *H* show normal respirations at 116 and 148 minutes, respectively. Animal survived. Dog weight 8.25 Kg. Female. For further details see legend to figure 1.

CONCLUSIONS

According to the method for evaluating dose effect experiments, as reported by Litchfield and Wilcoxon, the ED_{50} in dogs receiving a single infusion of Etamon in 100 ml. of saline over a period of 30 minutes is 63.5 mg. per kilogram with a confidence limit range of 55.7 to 72.4 mg. per kilogram.

There was evidence of an accumulative toxicity following Etamon infusions in multiple small doses in the same dog. No accumulative toxicity seemed to occur if the doses were given two to three days apart.

The ED_{50} for dogs receiving Etamon in gradually increasing doses biweekly and weekly is the same as for dogs which received only a single dose.

Death following a lethal dose of Etamon was due, in all cases presented, to a central respiratory paralysis. Changes observed in the blood pressure and electrocardiogram of the dogs receiving Etamon resemble those seen with anoxia. These changes were easily reversed if an adequate air intake was achieved.

Recovery from the respiratory paralysis which occurred after the administration of a lethal dose of Etamon was noted in those animals whose respiratory function was maintained by artificial means for a period of time sufficient to permit excretion of the Etamon. Of all methods tried in this connection only intermittent controlled positive pressure respirations could achieve any lasting satisfactory results. Others gave only transient aid or no aid at all.

Although manual artificial respiration would probably be effective in a human subject in whom there is a respiratory paralysis following Etamon infusion, the awkwardness of the method, the small amount of air that is moved with each excursion, and the strenuousness of the task leave much to be desired.

It is our feeling that deaths resembling the second one reported by McLemore and coworkers could probably be prevented by tracheal intubation and the use of a Drinker respirator or intermittent controlled positive pressure respiration for several hours. Oxygen, adrenaline, and other stimulants would serve as useful adjuncts.

Although the use of Prostigmin as an antagonist to Etamon in dogs and humans has been reported in the literature,[3] the infusion of this drug following a lethal dose of Etamon does not bear this out. Due to its additive effect upon the bradycardia seen with the anoxia incident to the respiratory paralysis, it is our feeling that, in the presence of a respiratory paralysis, the administration of Prostigmin would be deleterious rather than advantageous.

REFERENCES

[1] McLemore, G. A. Jr., Green, H. D., and Lide', T. M.: Respiratory complications from tetraethyl ammonium ion: Report of two deaths. Circulation **4:** 47, 1951.

[2] Litchfield, J. T. Jr., and Wilcoxon, F.: A simplified method for evaluating dose effect experiments. J. Pharmacol. & Exper. Therap. **95:** 99, 1949.

[3] Reardon, M. J., Marzoni, F. A. and Hendrix, J. P. The effect of neostigmine (Prostigmine) on the actions of tetraethylammonium (Etamon). Federation Proc. **6:** 364, 1947.

Further Studies on the Effects of Changes in the Distribution of Extracellular Fluid on Sodium Excretion

Observations Following Compression of the Legs

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Bandaging of the legs of sitting subjects resulted in an increase in the renal excretion of sodium which declined after the bandages were removed. Consistent results were not obtained in recumbent subjects. The findings appear to constitute further evidence that the distribution, rather than the total volume of extracellular fluids, has a regulatory action on sodium excretion.

WITHIN the past few years it has been repeatedly suggested that the sodium retention occurring in patients with circulatory failure (both cardiac and peripheral) was the result of inadequacy of cardiac output. Such inadequacy has been thought by some to cause sodium retention as the result of decline in glomerular filtration.[1, 2, 9, 10] Others have assumed that the retention was due to increased tubular reabsorption brought about in some manner by defective cardiac output.[3, 4, 11] Both concepts are attractive because they offer simple and reasonable explanations for decline in sodium excretion in such clinically diverse states as bleeding peptic ulcer, intestinal obstruction, and congestive heart failure. However, the previously reported studies of the present series[5–8] have offered what appears to us to be convincing evidence against the ideas of inadequate cardiac output, and of decline in glomerular filtration, as physiologic mechanisms responsible for sodium retention in normal subjects. It has been shown in healthy young males that the three functions (cardiac output, glomerular filtration, and sodium excretion) undergo independent alterations. Thus the change from recumbency to sitting caused marked decline in sodium excretion, slight decline in cardiac output, and no consistent change in glomerular filtration.[7, 8] Compression of the neck of sitting subjects caused elevation of sodium output, the other two functions remaining unaffected.[5, 7] Removal of small amounts of blood from sitting subjects produced decline in sodium excretion without alterations in glomerular filtration or cardiac output. When larger amounts of blood were removed, marked decrease in sodium excretion and slight decline in glomerular filtration were encountered without significant alterations in cardiac output.[6] On the other hand, the administration of digitalis to normal subjects caused early decline in cardiac output, the sodium excretion remaining constant or increasing slightly. As cardiac output returned to the normal level, decline in sodium excretion and in glomerular filtration usually occurred.[8] Thus studies on normal subjects lend no support to the concept that cardiac edema is the result of sodium retention consequent to forward failure. However, the possibility that these various findings in normal subjects may bear no relationship to the problem of heart failure cannot be excluded. The final answers to the question of the mechanism responsible for cardiac edema can only come from studying patients with heart failure. On the other hand most of the mechanisms of disease are exaggerations of normal mechanisms. Hence it seems probable that such studies will be more fruitful if conducted in the light of clear knowledge of the mechanisms

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regulating sodium and water balance in normal subjects.

There are a number of observations which suggest that alterations in the volume of body fluids may have an important regulatory effect on the renal output of sodium. Thus Peters[16] has suggested that disturbances in the Starling equilibrium between oncotic and capillary pressures lead to increased transudation into the tissues, and that the consequent decline in blood volume initiates sodium retention by means of unknown mechanisms. However, this concept is difficult to reconcile with the findings in patients with congestive heart failure, who may retain sodium in spite of well marked evidence of hypervolemia. Similar objections apply to the suggestion of Welt and Seldin,[12] that increased oncotic pressure of the plasma consequent to escape of fluid from the blood stream into the tissues may be the stimulus responsible for sodium retention. Patients with nephrosis retain sodium in spite of marked decrease in oncotic pressure.

Further evidence against the idea that decline in blood volume is an important stimulus to sodium retention is furnished by the observations of Goodyer and co-workers[18] and of Welt and Orloff.[13] These observers found that sodium excretion of normal subjects declined following the administration of hypertonic albumin solution, a procedure which would be expected to increase the blood volume at the expense of the interstitial fluid.

The possibility that decline in the total volume of interstitial fluid (rather than the plasma volume) constitutes a normal stimulus to sodium retention merits consideration. This concept is compatible with the decline in sodium output occurring after the administration of hypertonic albumin solutions. However, it is not compatible with the tendency of markedly edematous patients to retain sodium.

The foregoing considerations are susceptible of several alternative interpretations: (1) Deficit of the total volume of extracellular fluid causes sodium retention in healthy subjects, but this mechanism is not operative in edematous patients. (2) The stimulus to sodium retention is not decline in the volume of extracellular fluid but some closely related function. The first assumption seems unlikely on a priori grounds. The second assumption is favored by a considerable body of recent evidence, which may now be reviewed briefly.

It has been shown that experimental venous congestion of the legs of normal subjects causes a pronounced decline in sodium output.[14, 17] On the other hand, experimental congestion of the head of sitting subjects has the reverse effect.[5] These observations plus the effects of posture, bleeding, and digitalis, as considered in our previous communications,[5-8] can all be explained by a single hypothesis: that decline in the intracranial extracellular fluid volume (or some closely related function) leads to sodium retention. If such a regulating mechanism exists, it may possibly be of importance in relation to sodium retention in edematous states. These can only be proved by studies on patients with various types of edema. However, such studies are more likely to be fruitful if conducted in the light of a thorough knowledge of the normal physiology of the mechanisms concerned. Hence we have preferred to continue our investigations of healthy persons before studying patients.

It is well known that the intravenous injection of solutions containing sodium is soon followed by an increase in the urinary output of sodium.[20] Such an effect has naturally been assumed to be the result of an increase in the total volume of extracellular fluid. However, it might equally well be the result of a local increase in extracellular fluid volume in some regulatory area. Likewise, experimental congestion of the legs decreases sodium output, while experimental congestion of the head (carried out under appropriate conditions) has the reverse effect. These findings can, likewise, be explained by the assumption of alterations in extracellular fluid volume in an intracranial center. They raise the question whether alterations induced by redistribution of extracellular fluid from the legs to the remainder of the body might not tend to increase sodium excretion. The experiments to be reported in this communication were conducted in order to test this idea.

Method of Study

The procedure was similar to that previously reported.[7] The subjects were healthy male medical students. They ingested their usual diets to which 2 Gm. of sodium chloride were added daily. For at least two days prior to the experiment they avoided activities which would tend to disturb their usual fluid and electrolyte balance. On the day of the experiment breakfast was omitted. Subjects were allowed 30 Gm. of milk chocolate every hour, so as to prevent hunger from becoming a disturbing factor. One cigarette per hour was smoked by those subjects who so desired.

The subjects ingested 200 ml. of 0.14 per cent sodium chloride solution at hourly (recumbent) or half-hourly (sitting) intervals. Urinary output was measured hourly. The specimens for the first two hours were discarded, because it has been shown that equilibrium is not usually obtained until the third hour. Urinary and serum sodium concentrations were determined with the flame photometer, by the method of Mosher and co-workers.[19] In control experiments the subject continued to ingest the solution and to void at hourly intervals for a period of nine hours. In other observations the feet, legs, and thighs were snugly compressed by an elastic bandage at the end of the third hour after the onset of loading. The bandages were kept in place for four hours and then quickly removed, urine being collected for two additional hours.

Results

One subject developed migraine on two different occasions and exhibited different responses from those obtained in the other individuals. The data from this individual will be considered separately.

Table 1.—*Sodium Excretion of Normal Subjects in the Sitting Position Before, During, and After Compression of the Legs*

Subject	Control Hour	Experimental Period Legs Compressed				Postexperimental Control Period Legs Not Compressed		Serum Sodium mEq./liter	
	3rd Hr.	4th Hr.	5th Hr.	6th Hr.	7th Hr.	8th Hr.	9th Hr.	3rd Hr.	7th Hr.
Sodium Excretion (mEq./hr.)									
J.A.L.(1)	2.21	3.99	17.11	12.30	6.50	1.81	2.59	152	
J.A.L.(2)	2.81	6.50	6.75	3.88	3.63	2.45	1.41	148	
K.L.Y.	18.70	19.41	24.42*	25.95	25.59	19.13	15.01	140	
M.C.	13.80	17.11	18.60	13.33	10.48	8.59	11.84	—	—
C.P.C.	14.60	12.82	15.84	15.17	16.76	15.54	10.89	146	141
D.P.	12.15	16.06	15.03	19.00	13.46	12.60	10.55	137	143
L.L.S.	8.50	16.78	17.73	18.73	21.50	19.17	—	151	148
Average	10.39	13.24	16.49	15.48	13.99	11.33	8.72	144.7	144.0
Urine Volume (ml./hr.)									
J.A.L.	425	384	398	300	260	348	291		
J.A.L.	419	197	270	323	341	223	215		
K.L.Y.	390	461	520	617	448	368	442		
M.C.	445	398	620	325	419	318	592		
C.P.C.	443	427	511	410	399	457	495		
D.P.	434	462	401	481	350	323	315		
L.L.S.	607	408	572	446	512	270	294		
Average	452	391	471	415	390	329	378		

* Bandages readjusted and tightened at end of 5th hour.

During the control experiment in which the legs were not wrapped, the sodium output exhibited relatively small changes after the third hour of ingesting the loading solution. Since these data are similar to those previously reported,[5–8] they need not be considered further.

The effects of bandaging the legs of sitting subjects were studied in seven experiments (table

1, fig. 1). In one instance (subject C.P.C.) the results were inconclusive, while in the remaining six instances a slight to marked rise in sodium excretion occurred. The increment was least during the first hour, greatest during the second, and somewhat reduced during the third and fourth hours (fig. 1). Following removal of the bandages the sodium output declined, and sometimes to levels lower than those found prior to the application of the bandages. The average sodium output, which was approximately equal to the intake during the control hour, exceeded the intake by about 65 per cent while the legs were wrapped.

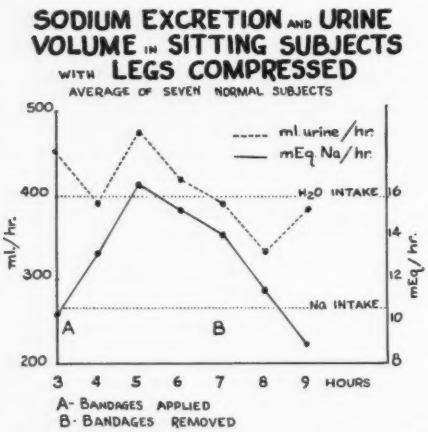

FIG. 1. Sodium excretion and urine volume of normal subjects in the sitting position with legs compressed. The bandages were applied immediately after collection of third hour urine specimen, and were removed immediately after seventh hour specimen was collected. The graph above represents the mean values obtained from seven observations on six subjects. The values for the first two hours are not included, since it was found that subjects did not reach constancy until the third hour. Sodium intake was 10.58 mEq. per hour, and water intake was 400 ml. per hour. Urine volume showed no consistent changes. On the other hand, the sodium output rose sharply after the application of the bandages, and reached a maximum in two hours. During the remaining two hours in which the legs were compressed, sodium output declined slightly from the peak value. After removal of the bandages a marked drop in sodium excretion was observed.

The similarity of the hourly changes in sodium excretion produced by wrapping the legs and by compression of the neck—as observed in a previous study[7]—was striking, and is illustrated in figure 2.

In the three subjects in which serum sodium was determined, both before and after compression of the legs, the values showed no consistent change (table 1). In two of the subjects there was a decrease of 3 and 5 mEq. per liter. In the third subject the serum sodium rose 6 mEq. per liter.

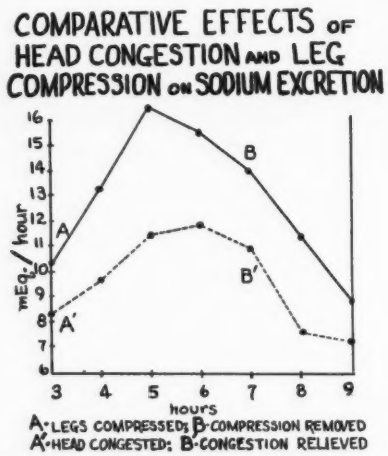

FIG. 2. Comparative effects of congestion of the head and compression of the legs on sodium excretion of normal subjects. The curve showing the effect of compression of the legs on hourly sodium output is the mean of seven observations on six healthy males (solid line). The curve showing similar changes effected by congestion of the head is the mean of observations on four healthy males (dotted line).[7] The experimental procedure was the same in both experiments, with the exception of sodium intake. With compression of the legs the sodium intake was 10.58 mEq. per hour; and with congestion of the head 9.58 mEq. per hour. The similarity of the two curves is striking. Both show a marked rise during the first two hours after either compression of the legs or congestion of the head, and then a decline during the latter part of the observation period (A–B, A′–B′). Both curves show a decline of sodium excretion to levels below control values in the two hours following removal of compression of legs (B) or relief of congestion of the head (B′).

The effects of wrapping the legs of recumbent subjects were observed in three experiments (table 2). No consistent changes were observed in urine volume. The sodium excretion was greater than the intake (5.76 mEq. per hour),

TABLE 2.—*Sodium Excretion and Urine Volume of Normal Subjects in Recumbent Position with Legs Compressed*

Subject	Control Hour	Experimental Period Legs Compressed				Postexperimental Control Period Legs not Compressed		Serum Sodium mEq./liter	
	3rd Hr.	4th Hr.	5th Hr.	6th Hr.	7th Hr.	8th Hr.	9th Hr.	3rd Hr.	7th Hr.
Sodium Excretion (mEq./hr.)									
J.A.L.	7.83	22.64	19.11	19.04	15.96	12.63	14.21	156	
D.P.	14.5	9.4	21.9	13.8	10.06	11.1	—	146	143
M.C.	22.4	19.1	21.1	16.9	14.3	—	13.9	141	140
Average	14.21	17.05	20.70	16.58	13.62	11.87	14.06	143.5	141.5
Urine Volume (ml./hr.)									
J.A.L.	412	333	147	272	228	183	145		
D.P.	127	77	196	96	266	90	—		
M.C.	295	238	224	368	223	—	310		
Average	278	216	189	245	239	137	228		

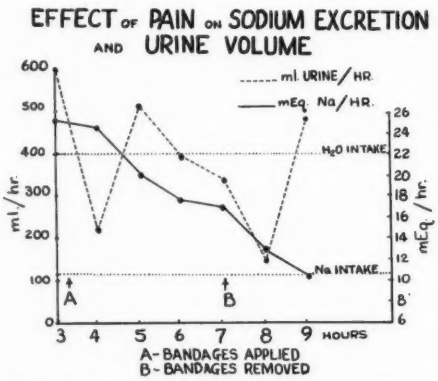

FIG. 3. Effect of pain on sodium excretion and urine volume of subject in sitting position with legs compressed. Just prior to the application of the bandages, venepuncture was performed for determination of serum sodium (A). Within 10 to 15 minutes after the application of bandages subject developed a severe throbbing headache in the left temporal area, which could be relieved by pressure over the left temporal artery. The headache spread to the right temporal area, and decreased somewhat in intensity, but persisted throughout the experiment. The hourly sodium output (solid line) decreased consistently during the experiment. Unlike the changes shown in figure 1, there was no rise in sodium output after compression of the legs, indicating that the antinaturetic effect of pain outweighs the naturetic effect of compression of the legs in the absence of headache (fig. 1). After an initial drop in urine volume the hourly output rose moderately but fell again after a second venepuncture at B. This illustrates the antidiuretic effect of a painful procedure.

as is usual with recumbent subjects.[5] However, no consistent changes in sodium excretion were noted. Here again, there is a similarity of hourly changes in sodium excretion observed after wrapping the legs, and congestion of the head.[5] Noteworthy changes in serum sodium values were not observed.

The effects of pain on sodium excretion. The findings are illustrated in figure 3. The subject developed a spontaneous attack of migraine shortly after the bandages were applied to the legs. The severe headache persisted throughout the experimental period, and was accompanied by a striking progressive decline in sodium excretion and a somewhat less pronounced decrease in urine volume (fig. 3). On another occasion the needle became plugged during an attempted venepuncture on the same subject. The resulting hematoma caused considerable discomfort and was followed by a milder attack of migraine. The sodium output declined in this experiment, the degree of decline being less than during the more severe attack of migraine.

DISCUSSION

The data indicate that bandaging of the legs causes increased output of sodium in the urine. In view of the other observations which have been mentioned, it appears probable that the effect is analogous to that produced by an in-

travenous infusion of saline solution, and is due to an increase in the volume of extracellular fluid in some regulatory area.

The observations are in accord with numerous other findings in pointing toward a lack of correspondence between the renal excretion of sodium and of water.

The similarity in sitting subjects between the effects on sodium excretion of wrapping the legs and of compressing the neck (fig. 2) has already been mentioned. In each instance sodium excretion increased for two to three hours, and then gradually declined during the last of the procedure. The resemblance between the two curves may be fortuitous, but it is also possible that in both instances the effects were mediated by an increase in the extracellular fluid volume in the brain induced by distributional changes in the interstitial fluid. In this connection, it is of interest that in recumbent subjects neither compression of the neck[5] nor bandaging the legs had any consistent effect on sodium excretion (table 2). The reasons for the differences between the effects of these procedures in the sitting and the recumbent posture are not clear at this time.

Further information is, likewise, needed in order to interpret the time curves of sodium excretion. The various procedures which are believed to alter sodium excretion by affecting intracranial fluid volumes have usually exhibited a definite lag of more than one hour before the maximal effect is apparent. This makes both a direct neurogenic mechanism and an adrenal cortical mechanism seem unlikely, the peak effect being too slow for the former and too rapid for the latter. The reasons for the failure of sodium excretion to remain at the maximal level during the third and fourth hours (figs. 1 and 2), despite the continued presence of the procedure which led to the increase, are, likewise, not clear. Presumably, the displacement of extracellular fluid from the legs was more rapid in the first two hours than subsequently, and the autoinfusion of saline solution proceeded more slowly in the subsequent period. If, however, the increase in sodium excretion was the result of an increment in interstitial fluid in the cranial cavity, it is difficult to understand why such increment should be of lesser magnitude during the third and fourth than during the second hour of leg compression. Here again, additional evidence is needed.

The starting point of these experiments was the desire to study the effect of alterations in the distribution of body fluids on sodium excretion. The demonstration of a pronounced increment when the legs were compressed constitutes further evidence, in addition to that already cited in the introduction, that alterations in distribution of body fluids without alterations in total volume may exert pronounced effects on sodium excretion.

If, as seems likely from the present and the preceding observations,[5–8] changes in the distribution of body fluids are capable of exerting a regulatory effect on sodium excretion, the question naturally arises as to which fluid compartment is concerned. Evidence against the volume or distribution of blood plasma as a stimulus to the regulation of sodium excretion has already been cited.[13] It seems unlikely that compression of the legs would result in a significant displacement of intracellular fluid. Furthermore, if increase in intracellular fluid in some regulatory area were more important than increase in extracellular fluid in causing augmentation of sodium excretion, one would expect that the administration of water (which diffuses freely into the intracellular compartment) would be a more effective natriuretic measure than the administration of solutions of sodium chloride. Such is not the case. On the contrary, ingestion of large amounts of water may actually lead to depression of sodium excretion.[20]

Most of the data in the literature, as well as our own previous observations, appear to be compatible with the concept that alterations in the volume of the intracranial interstitial fluid lead to similar directional changes in sodium excretion. However, the demonstration that tilting the head downward does not increase sodium excretion, and that compression of the neck or legs (which augments sodium output of sitting subjects) has no consistent effect on recumbent subjects,[5, 7] would appear to be opposed to this concept. The problem is

complex because the cranial cavity is a rigid box containing four fluid compartments instead of the usual three. Methods for measurement of the intracranial content of intracellular, interstitial, intravascular, and cerebro spinal fluid are not available. It is possible that in the sitting subject compression of the neck increases the interstitial fluid, while in the recumbent subject one of the other fluids is increased. More knowledge is, therefore, necessary before final conclusions can be drawn concerning the precise relationship between the volume of these several intracranial fluids and the control of sodium output.

In order that this discussion should not be misinterpreted, two points mentioned in previous reports merit re-emphasis. The first is that the intracranial mechanism under discussion is certainly not the only one, and is probably not the most potent mechanism regulating the renal excretion of sodium. Such factors as the endocrine balance of the subject, the presence or absence of discomfort or emotional stress, the degree of consciousness, the level of plasma sodium, and (probably most important) the state of the sodium stores of the body (that is, the balance between intake and loss during the several preceding days) are probably of great importance in determining sodium output. Further investigations are needed before the complexities of the interplay of these and other unknown variables can be understood.

A second point which merits re-emphasis is that the investigations thus far made on the relationship between the distribution of body fluids and the excretion of sodium have been limited to normal subjects. There is as yet no proof that the mechanisms under discussion play a role in edematous states, or in other diseases connected with alterations of sodium excretion.

Summary

Compression of the legs of healthy young males in the sitting position, by means of an elastic bandage, causes well marked increment in urinary sodium output. No consistent effect was found in the recumbent position. Urine volume was not significantly altered.

Pain, due to migraine or to unsuccessful venepuncture with the formation of a local hematoma, was attended by a pronounced decline in the output of sodium and a less marked decrease in urine volume.

The possible mechanism of these results has been discussed. It is believed that the augmentation of sodium excretion is due to redistribution of extracellular fluid from the legs to certain regulatory areas. Compression of the legs is, therefore, considered to be analogous to the intravenous administration of saline solution. The data are considered as being compatible with the previously suggested concept of an intracranial center, sensitive to alterations in the local volume of interstitial fluid, and exerting a regulating influence on extracellular fluid volume by altering sodium excretion.

REFERENCES

[1] Merrill, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as primary cause of edema. J. Clin. Investigation **25:** 389, 1946.

[2] Makotoff, R., and Ross, G.: Renal blood flow and sodium excretion studies in congestive heart failure (abstract). J. Clin. Investigation **26:** 1190, 1947.

[3] Briggs, A. P., Fowell, D. W., Hamilton, W. F., Remington, J. W., Wheeler, N. C., and Winslow, J. A.: Renal and circulatory factors in the edema formation of congestive heart failure. J. Clin. Investigation **27:** 810, 1948.

[4] Kattus, A. A., Sinclair-Smith, B., Genest, J., and Newman, E. V.: The effect of exercise on the renal mechanism of electrolyte excretion in normal subjects. Bull. Johns Hopkins Hosp. **84:** 344, 1949.

[5] Lewis, J. M., Buie, R. M., Sevier, S. M., and Harrison, T. R.: The effect of posture and of congestion of the head on sodium excretion in normal subjects. Circulation **2:** 822, 1950.

[6] Lombardo, T. A., Eisenberg, S., Oliver, B. B., Viar, W. N., Eddleman, E. E., and Harrison, T. R.: Effect of bleeding on electrolyte excretion and on glomerular filtration. Circulation **3:** 260, 1951.

[7] Viar, W. N., Oliver, B. B., Eisenberg, S., Lombardo, T. A., Willis, Kathryn, and Harrison, T. R.: The effect of posture and of compression of the neck on excretion of electrolytes and glomerular filtration: further studies. Circulation **3:** 105, 1951.

[8] Greve, M. J., Eddleman, E. E., Willis, Kathryn, Eisenberg, S., and Harrison, T. R.:

The effect of digitoxin on sodium excretion, creatinine clearance and apparent cardiac output. Circulation **3:** 405, 1951.

[9] MOKOTOFF, R., ROSS, G., AND LEITER, L.: Renal plasma flow and sodium reabsorption in congestive heart failure. J. Clin. Investigation **27:** 1, 1948.

[10] PITTS, R. F., AND DUGGIN, J. J: Studies on diuretics. II. The relationship between glomerular filtration rate, proximal tubular reabsorption of sodium and diuretic efficacy of mercurials. J. Clin. Investigation **29:** 372, 1950.

[11] BORST, J. G. G.: The maintenance of an adequate cardiac output by the regulation of the urinary excretion of water and sodium chloride. An essential factor in the genesis of edema. Acta med. scandinav. Suppl. 207, 1948.

[12] WELT, L. G., AND SELDIN, D. W.: The pathologic physiology and treatment of edema. Veterans Adm. Tech. Bull. TB 10–69, Jan. 12, 1951.

[13] —, AND ORLOFF, J.: Effects of infusion of albumin and electrolytes in normal subjects. J. Clin. Investigation **28:** 818, 1949.

[14] WILKINS, R. W., CULBERTSON, J. W., BELTON, A. B., TINSLEY, C. M., JUDSON, W. E., AND BURNETT, C. H.: Antidiuresis and renal vasoconstriction following venous congestion of the limbs in normal hypertensive and splanchnicectomized subjects. J. Clin. Investigation **28:** 819, 1949.

[15] VERNEY, E. B.: Absorption and excretion of water; the antidiuretic hormone. Lancet **2:** 739, 781, 1949.

[16] PETERS, J. P.: The role of sodium in the production of edema. New England J. Med. **239:** 353, 1948.

[17] JUDSON, W. E., EPSTEIN, F. H., TINSLEY, C. M., BURROWS, B. A., AND WILKINS, R. W.: The hemodynamic and renal functional effect of venous congestion of the limbs in patients with diabetes insipidus. J. Clin. Investigation **29:** 826, 1950.

[18] GOODYER, A. V. N., PETERSON, E. R., AND REDMAN, A. S.: Some effects of albumin infusions on renal function and electrolyte excretion in normal man. J. Applied Physiol. **1:** 671, 1949.

[19] MOSHER, R. E., BOYLE, A. J., BIRD, E. J., JACOBSON, S. D., BATCHELOR, T. M., ISERI, L. T., AND MYERS, G. W.: The use of flame photometry for the quantitative determination of sodium and potassium in plasma and urine. Am. J. Clin. Path. **19:** 461, 1949.

[20] TAYLOR, N. B.: The excretion of urine. In Best, C. H., AND TAYLOR, N. B.: The Physiological Basis of Medical Practice, ed. 5. Baltimore, Williams & Wilkins, 1950, P. 457.

The Relation of Water and Sodium Excretion to Blood Pressure in Human Subjects

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High sodium loads were administered intravenously to a group of subjects whose blood pressures covered a wide range. Despite large individual variations, the water and sodium excretion of the group were found to be significantly and directly correlated with blood pressure.

THE RELATION of salt to hypertension has been the subject of investigation since the report of Ambard and Beaujard in 1904.[1] Over the years, numerous investigators have adduced evidence that high sodium intakes tend to increase blood pressure,[2–7] while sodium restriction, either by dietary measures,[8–14] or ion exchange resin administration[15, 16] may be associated with a lowering of pressure, although the number of hypertensive patients who so respond is limited and clinical improvement often exceeds the reduction in pressure.[13, 14]

These relationships have been viewed as evidence that the development or maintenance of essential hypertension may involve the adrenal cortex,[17, 18] presumably through the operation of its so-called "sodium retaining" hormones. Surprisingly little attention seems to have been devoted to the exploration of this hypothesis by actual measurements of the rates at which hypertensive patients excrete sodium relative to normotensive controls. Perera and Blood[17] reported that a group of hypertensive patients exhibited a smaller diuresis than a corresponding group of controls during a 24 hour period of salt restriction. Considerable overlap was present, however, and the sodium output of the two hypertensives in which this factor was measured was not different from the output of two normotensive controls. Farnsworth and Barker[19] studied the simultaneous chloride and inulin clearances of 10 hypertensive patients as compared with 12 controls. At comparable filtration rates, the reabsorption of chloride (and, presumably, sodium) was lower in the hypertensive group. Differences in dietary salt intake prior to the studies were assumed to be inconspicuous, but were not measured.

The present experiments were designed to study over a wide pressure range the relationship of the blood pressure level to sodium clearance and excretion rates in response to a fixed sodium load.

Methods and Materials

The subjects for these studies consisted of 45 patients from the wards and outpatient department of the Evanston Hospital. The majority were suffering from some form of cardiovascular disease (table 1). The group included 14 patients with a history of chronic congestive failure, who were well controlled at the time of study.

No dietary restrictions were imposed except that the subject was instructed to take nothing by mouth from the prior midnight until completion of the test. Upon reporting to the laboratory at 7:30 a.m., height and weight were measured and the surface area was calculated. The patient was placed at bed rest and catheterized. The bladder was drained, washed with two 10 cc. portions of sterile distilled water and blown out with two 20 cc. portions of air. The specimen and washings from this collection were discarded. The catheter was clamped and left in place.

At the end of a 30 minute control period the urine was collected by the procedure outlined above, the volume measured and the specimen saved for analysis. During this period, control blood samples were taken.

Following the control period, 100 cc. per square meter of body surface area of a 5 per cent sodium chloride solution were infused into an arm vein over a 25-minute interval. Urine collections were made at 30, 60, 90, 120 and 180 minutes, respectively from the time of the start of the infusion. Blood samples were taken at the end of the first period and at the midpoint of all succeeding periods.

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Urine and blood samples were analyzed for sodium concentration by use of the Beckman flame photometer. Hematocrit determinations were done on all blood samples. Eosinophil counts were made during the control period and one hour after the start of the infusion.

From these measurements the sodium concentration, water and sodium excretion rates and sodium clearance were calculated for the control period and each of the test periods. The cumulative water and sodium excretions from the start of the infusion were also calculated.

TABLE 1.—*Composition of the Subject Group*

Diagnosis	Number of Subjects	
No circulatory disease		3
Rheumatic heart disease		4
Essential hypertension		8
Hypertensive heart disease		18
Without history of failure	9	
With history of failure	9	
Arteriosclerotic heart disease		12
Without history of failure	7	
With history of failure	5	
Total		45

TABLE 2.—*Mean Age, Renal Function and Hematocrit Values in Subjects Grouped According to Mean Blood Pressure Range*

Mean Pressure Range (mm. Hg)	No. of Subjects	Age (yrs.)	PSP Excretion (%)	Maximum Concentration (S. G.)	Hematocrit (vol. %)
70- 99	5	38	52	1.024	42
100–119	13	63	58	1.021	46
120–139	15	64	62	1.018	43
140–199	12	59	52	1.018	44

The blood pressure of the subject was taken at intervals throughout the procedure by use of a mercury sphygmomanometer. The blood pressure readings were averaged and the approximate mean pressure estimated by adding together the mean systolic and diastolic pressures and dividing the sum by two. The value obtained by this procedure is usually somewhat higher than the true mean pressure as obtained by the analysis of pressure pulse curves.[20]

At a time other than the test day, renal function was estimated by means of a phenolsulfonphthalein (PSP) excretion test and a determination of the maximum concentrating capacity.

The existence and degree of correlation between any two factors were determined by the calculation of regression and correlation coefficients. Adjustments were made for the influence of a third factor by the application of the technic of regression on the third variable.[21] The relation of blood pressure to other factors was further investigated by grouping the subjects into four blood pressure ranges based on the frequency distribution of the mean pressures (table 2). The significance of differences between groups was estimated by determining the standard error of the differences between means or regression coefficients. Statistical significance was established by application of Student's t tests.[22]

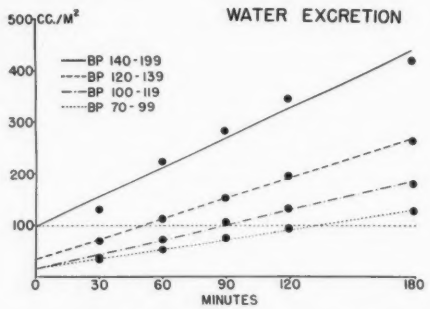

FIG. 1. Cumulative water excretion following the administration of 5 per cent sodium chloride solution, 100 cc. per square meter, in 25 minutes, starting from zero time. The 45 human subjects have been divided into four groups based on their approximate mean blood pressure during the experiment. The t values for the differences in regression coefficients of water excretion on time (b) between adjacent groups are significant ($p<0.01$).

b (70– 99) = 0.63 b (130–139) = 1.30
b (100–129) = 0.94 b (140–199) = 1.91

RESULTS

When the cumulative water and sodium outputs of the four groups were compared, it was found that the higher the blood pressure range, the greater were the amounts excreted (figs. 1 and 2). Comparison of the slopes of the curves relating output to time indicated that the differences between groups were real ($p < 0.01$).

The differences in behavior at the various blood pressure ranges were quite striking. By the end of three hours, the group in the highest range excreted more than four times the amount of administered water while the patients in the lowest range excreted about one-quarter more than the quantity received. During this same interval, the group in the

highest range had eliminated virtually all of the administered sodium, a quantity almost three times as great as that excreted by the subjects in the lowest range.

The relationship between blood pressure and the amounts of water and sodium excreted was evaluated also by correlating the three hour excretion of each patient with the pressure (table 3). Although the relatively low values of the correlation coefficients indicated considerable variability, the total number of patients studied was sufficiently large to permit the establishment of meaningful regressions ($p < 0.01$).

Analysis of the rates at which water and sodium were excreted showed that the maxima were achieved during the first period after the start of the infusion with a subsequent decline toward the control rate for sodium and below that for water (table 3). The correlation of individual excretion rates with blood pressure was significant in each test period ($p < 0.01$). The control rates of water and sodium excretion were related to blood pressure also, although to a lesser degree ($p < 0.05$).

The urinary sodium concentration increased progressively throughout the test. During no period was a significant relation to blood pressure demonstrated.

The greater sodium excretion at higher blood pressures primarily reflected the rise in sodium clearance, most evident during the first hour after the start of the sodium chloride infusion (fig. 3, table 3). At low pressure levels, the

TABLE 3.—*Relation of Blood Pressure to Urinary Output of Water (V) and Sodium ($U_{Na}V$), Sodium Concentration (U_{Na}) and Clearance Rate $\frac{(U_{Na}V)}{P_{Na}}$ before and after Intravenous Infusion of 5 Per Cent Sodium Chloride Solution, 100 cc per Square Meter of Body Surface, in 25 Minutes*

Dependent Variable Correlated with BP (mm. Hg)	Measurement Period (start of infusion is zero time)								
	(−30 to 0 min.)			(0 to 30 min.)			(30 to 60 min.)		
	mean	b	r	mean	b	r	mean	b	r
V (cc./min./m.²)	1.22	.018†	.414†	2.46	.040†	.556†	1.71	.028†	.544†
adjusted for age:					.044†	.585†			
$U_{Na}V$ (mM./min./m.²)	0.15	.0016*	.315*	0.38	.0060†	.554†	0.37	.0056†	.504†
adjusted for age:					.0068†	.581†			
U_{Na} (mM./L.)	148.	−.583	−.224	162.	−.034	−.017	216.	−.325	−.167
$\frac{U_{Na}V}{P_{Na}}$ (cc./min./m.²)	0.96	.013*	.366*	2.38	.036†	.537†	2.41	.036†	.492†
adjusted for age:					.040†	.571†			

Dependent Variable Correlated with BP (mm. Hg)	Measurement Period (start of infusion is zero time)											
	(60 to 90 min.)			(90 to 120 min.)			(120 to 180 min.)			(0 to 180 min.)		
	mean	b	r	mean	b	r	mean	b	r	mean	b	r
V (cc./min./m.²)	1.37	.013†	.435†	1.31	.013†	.436†	1.02	.009†	.459†	1.51	.019†	.573†
adjusted for age:												
$U_{Na}V$ (mM./min./m.²)	0.30	.0025†	.397†	0.30	.0028†	.421†	0.25	.0024†	.484†	0.31	.0033†	.515†
adjusted for age:												
U_{Na} (mM./L.)	224.	.087	.036	227.	−.159	−.084	240.	−.420	−.225			
$\frac{U_{Na}V}{P_{Na}}$ (cc./min./m.²)	1.93	.015*	.383*	2.00	.021†	.471†	1.68	.011	.326*			
adjusted for age:												

b = coefficient of regression on blood pressure.
r = coefficient of correlation with blood pressure.
* = $p < 0.05$ that b or $r = 0$.
† = $p < 0.01$ that b or $r = 0$.

sodium clearance rose to about twice the control value and tended to remain constant thereafter. At higher pressure ranges, the sodium clearance was increasingly elevated, and exhibited a secondary fall during the second and third hours. At the highest pressure range, these opposing trends resulted in a sharp peak

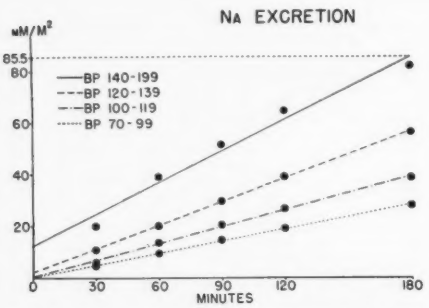

FIG. 2. Cumulative sodium excretion. Conditions as in figure 1. The t values for the difference in regression coefficients of sodium excretion on time (b) between adjacent groups are significant ($p < 0.01$).

b (70- 99) = 0.15 b (130–139) = 0.30
b (100–129) = 0.22 b (140–179) = 0.40

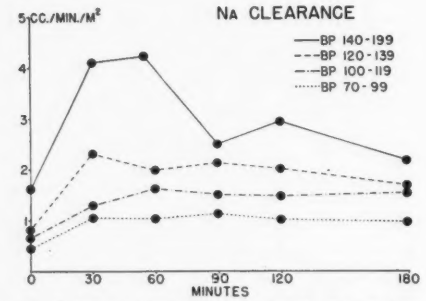

FIG. 3. Sodium clearance by periods. Conditions as in figure 1

in sodium clearance with a return toward the values exhibited by the lowest pressure group at the end of three hours.

The differences in sodium clearance between groups were not attributable to the rate at which hemodilution followed the infusion of the concentrated sodium chloride solution (fig. 4) or to the extent of change in plasma sodium concentration. The changes in hematocrit value were virtually identical at all blood pressure levels, particularly when adjustments were made for the initial value, which varied slightly between groups (table 2). The changes in plasma sodium concentration were comparable also.

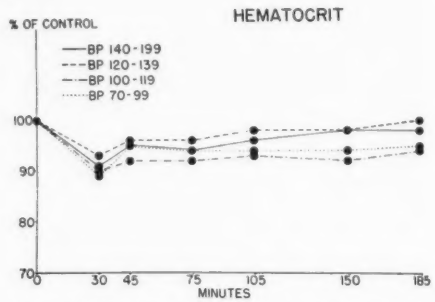

FIG. 4. Hematocrit changes by periods. For purposes of comparison, the control values for each group have been taken to equal 100 per cent. Test values are expressed as a percentage of the control. Conditions as in figure 1.

TABLE 4.—*Relation of Age and Renal Function to Sodium Excretion Rate (First Test Period) and to Mean Blood Pressure*

Independent Variable	Dependent Variable			
	$U_{Na}V$ (mM./min./m.²)		BP (mm. Hg)	
	b	r	b	r
Age (years)...	−.0016	−.224	.59	.330*
adjusted for BP:.....	−.0032	−.216		
PSP excretion (%).....	−.0005	−.060	−.36	−.150
adjusted for BP:.....	−.0036	−.142		
Maximum concentration (S.G.)....	1.46	.029	−117.88	−.255
adjusted for BP:.....	8.49	.199		

b = coefficient of regression of dependent on independent variable.
r = coefficient of correlation.
* = $p > 0.05$ that b or $r = 0$.

To determine the influence of age and renal function on the response to sodium loading, these factors were compared with the sodium excretion rate during the first test period, in which differences in rate were most marked. No meaningful relations were found (table 4),

even when the influence of blood pressure on excretion rates was adjusted for by regression technics.

Since blood pressure was significantly correlated with age ($p = 0.03$), although not with renal function in this subject group (table 4), the sodium and water excretion rates during the first test period were compared with blood pressure after any influence of age was adjusted for. This adjustment increased the extent of the relationship previously established (table 3).

A comparison of sodium excretion rates was also made between patients with and those without a previous history of congestive failure. Those patients who had experienced one or more episodes of failure excreted significantly less water and sodium under load at comparable blood pressure levels in both the primarily hypertensive ($p < 0.01$) and primarily arteriosclerotic ($p < 0.05$) classifications.

The eosinophil counts during the control period averaged 157 cells per cubic millimeter. During the test period this value fell about 25 per cent. The drop was not related to blood pressure differences.

Discussion

The results show that patients given equivalent sodium loads under the circumstances of these studies excreted water and sodium at rates which were significantly correlated with their approximate mean blood pressure during the test period. As a whole, our findings are consistent with the observations of Farnsworth and Barker relative to the reduced chloride reabsorption of hypertensive patients.[19] The low magnitudes of the correlation coefficients and the degree of variability within the various blood pressure ranges indicate that factors other than blood pressure strongly modify the response of the individual patient.

These findings are of interest in relation to the results of salt-selection and salt-loading studies in various forms of experimental hypertension. The chronically (but not the acutely) desoxycorticosterone acetate- (DCA) treated hypertensive rat voluntarily chooses more dietary sodium than untreated controls[23, 24] and excretes larger quantities of water and sodium, either under basal conditions or following sodium and water loads.[24] In contrast, the renal hypertensive rat voluntarily restricts its salt intake.[23, 25] The pattern of water and sodium excretion by human hypertensive patients thus tends to resemble that of the chronically desoxycorticosterone acetate–treated hypertensive animal.

The absence of a correlation between water and sodium excretion rates of this group of human hypertensives and their renal function, as judged by phenolsulfonphthalein (PSP) excretion and maximum concentrating capacity, also suggests that primarily renal factors did not materially influence their response to loading.

Summary and Conclusions

Equivalent water and sodium loads amounting to 100 cc. per square meter of body surface area of a 5 per cent sodium chloride solution were administered intravenously to 45 human subjects, none of whom was in acute congestive failure at the time of study.

The excretion of water and sodium over a three hour period was found to be significantly and directly related to the approximate mean blood pressure. The response to loading was not correlated with age, phenolsulfonphthalein excretion rate, or maximum concentrating capacity. Patients with a history of congestive failure exhibited significantly lower rates of excretion.

The behavior of the human hypertensive patient in response to salt loading is similar to that of chronically desoxycorticosterone acetate–treated hypertensive animals.

REFERENCES

[1] Ambard, L., and Beaujard: Causes of arterial hypertension. Arch. Gen. Med. **1:** 520, 1904.

[2] —, and Cahn, R.: Hypertension inducing action of salt. Bull. Soc. Med. hop. Paris. **50:** 77, 1926.

[3] Renaud, M.: Sodium citrate and arterial tension. Bull. Soc. Med. hop. Paris. **50:** 102, 1926.

[4] Berghoff, R. S., and Geraci, A. S.: The influence of sodium chloride on blood pressure. Illinois M. J. **56:** 395, 1929.

[5] Thompson, W. H., and McQuarrie, I.: Effects of various salts on carbohydrate metabolism and blood pressure in diabetic children. Proc. Soc. Exper. Biol. & Med. **31:** 907, 1934.

[6] McQuarrie, I.: The effect of excessive salt ingestion on carbohydrate metabolism and arterial pressure in diabetic children. Proc. Staff Meet., Mayo Clin. **10:** 239, 1935.

[7] DeWesselow, O. L. V. S., and Thompson, W. A. R.: A Study of some serum electrolytes in hypertension. Quart. J. Med. **8:** 361, 1939.

[8] Allen, F. M., and Sherrill, J. W.: The treatment of arterial hypertension. J. Metabol. Res. **2:** 429, 1922.

[9] Calvert, F. G. B.: The effect of sodium chloride intake on blood pressure. London Practitioner. **113:** 193, 1924.

[10] Bennett, D. W.: Sodium and potassium studies in persons with and without hypertension. J. Lab. & Clin. Med. **26:** 344, 1940.

[11] Kempner, W.: Treatment of kidney disease and of hypertensive vascular disease with rice diet. North Carolina M. J. **5:** 125, 1944.

[12] Grollman, A., Harrison, T. R., Mason, M. F., Baxter, J., Crampton, J., and Reichsman, F.: Sodium restriction in the diet for hypertension. J. A. M. A. **129:** 533, 1945.

[13] Kert, M. J., Rosenburg, M. J., Coodley, E. L., Murdock, L. J., Hoffman, S. H., Brotman, E. J., and Johnston, W. L.: Treatment of hypertension. J. A. M. A. **143:** 721, 1950.

[14] Corcoran, A. C., Taylor, R. D., and Page, I. H.: Controlled observations on the effect of low sodium dietotherapy in essential hypertension. Circulation **3:** 1, 1951.

[15] Page, I. H.: Treatment of essential and malignant hypertension. J. A. M. A. **147:** 1311, 1951.

[16] Griffith, R. S., Helmer, O. M., and Kohlstaedt, K. G.: Low sodium diet and resin therapy in hypertension. Federation Proc. **11:** 59, 1952.

[17] Perera, G. A., and Blood, D. W.: Disturbance in salt and water metabolism in hypertension. Am. J. Med. **1:** 602, 1946.

[18] —: The relationship of the adrenal cortex to hypertension; observations on the effect of hypoadrenalism on a patient with hypertensive vascular disease. J. A. M. A. **129:** 537, 1945.

[19] Farnsworth, E. B., and Barker, M. H.: Tubular resorption of chloride in hypertensive and in normal individuals. Proc. Soc. Exper. Biol. & Med. **52:** 74, 1943.

[20] Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 4. Baltimore, Williams & Wilkins, 1945. P. 120.

[21] Snedecor, G. W.: Statistical Methods, ed. 4. Ames, Iowa, Iowa State College Press, 1946. P. 126.

[22] Fisher, R. A.: Statistical Methods for Research Workers, ed. 10. London, Oliver and Boyd, 1946. pp. 122, 140.

[23] Tosteson, D. C., DeFriez, A. I. C., Abrams, M., Gottschalk, C. W., and Landis, E. M.: Effects of adrenalectomy, desoxycorticosterone acetate and increased fluid intake on intake of sodium chloride and bicarbonate by hypertensive and normal rats. Am. J. Physiol. **164:** 369, 1951.

[24] Green, D. M., Saunders, F. J., Van Arman, C. G., Calvin, L. D., and Sturtevant, F. M.: Mechanisms of desoxycorticosterone action (8): Temporal relationships of polyuria, polydipsia, sodium exchanges and hypertension. Am. J. Physiol. In press.

[25] Abrams, M., DrFriez, A. I. C., Tosteson, D. C., and Landis, E. M.: Self-selection of salt solutions and water by normal and hypertensive rats. Am. J. Physiol. **156:** 233, 1949.

Increased Urinary Urobilinogen Following Acute Myocardial Infarction

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A study was conducted of the serial urinary urobilinogen excretion in patients with acute myocardial infarction, using Watson's semiquantitative method. Increased excretion was observed in some 90 per cent of the subjects with infarcts confirmed by the electrocardiogram and in more than half of the subjects where the electrocardiogram was not conclusive. The degree and duration of increased urinary urobilinogen had no apparent bearing upon prognosis. It is postulated that the altered urobilinogen excretion is induced by hepatic effects of the stress reaction incident to acute myocardial infarction.

WATSON and associates[1] have provided a simple and rapid method for the semiquantitative determination of urine urobilinogen. In several of Watson's reports[1-3] he has indicated confirmation of Head's observation that acute myocardial infarction is usually followed in from 36 to 72 hours by the appearance of increased quantities of urobilinogen in the urine. We have been unable to find any published data extending or verifying these observations.

A satisfactory explanation for the altered excretion of urobilinogen is not available. It has been suggested that the pattern may be due to a hepatotoxin elaborated in the infarcted heart muscle, or to the vascular collapse and hypoxia associated with the acute myocardial infarction. It was deemed of interest to evaluate further the urinary excretion of urobilinogen in patients with proven or suspected myocardial infarction to determine its possible value in diagnosis or prognosis and to appraise the possible causative mechanisms.

CLINICAL MATERIAL AND METHODS

The subjects selected for study included 21 patients with acute myocardial infarction confirmed by the appearance of the classic pattern of injury and necrosis in the electrocardiogram, nine patients in whom acute myocardial infarction was suspected but not fully substantiated by the electrocardiogram, and 20 individuals selected as controls in whom there was no reason to suspect myocardial infarction, pulmonary infarction or liver disease. An additional positive control group consisted of seven patients with liver disease proven by laboratory studies. A final group consisted of three patients in whom pulmonary infarction was demonstrated. A total of 450 urine urobilinogen determinations were carried out in the 60 subjects. The information describing the groups of subjects is summarized in table 1.

As recommended[1] the urine specimen was collected over a two-hour period between 2:00 and 4:00 p.m., the patient having voided and taken 200 cc. of water by mouth at 2:00 p.m. The sample of urine was delivered to the laboratory promptly and analyzed by both Watson's[1] and Brereton and Lucia's[4] method, using the pontacyl standard in all instances. In most specimens higher values were obtained by the latter technic. However, since the former method has been more widely evaluated, the results reported herein are on the basis of this test (upper limit of normal, 1.0 Ehrlich unit). As has been indicated by others[4-7] the occurrence of a pink color in the blank interfered with the spectrophotometer* readings in some instances. This difficulty was corrected by altering the sodium acetate solution in accordance with instructions from Dr. Watson.[5] In some subjects, attendant upon the critical situation of the patient, there was difficulty in obtaining the specimens during the first and second days of the illness.

RESULTS AND COMMENT

In 19 of the 21 patients with acute myocardial infarction confirmed by the electrocardiogram, the urine urobilinogen exceeded

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* The Coleman Junior Model Spectrophotometer was used throughout.

1.0 Ehrlich unit at some time during the course of the illness. The highest percentage of positive results occurred on the third day after the attack and all specimens tested were negative by the twentieth day of the illness. The majority of the positive specimens appeared in the eight-day period after onset of the episode. When positive the level of urobilinogen often exceeded 2.0 units and ranged as high as 4.2 units (fig. 1).

An attempt was made to correlate the increased excretion of urobilinogen with the occurrence of shock, and with the presence or absence of cardiac decompensation. Of the 21 patients with confirmed infarction the blood

TABLE 1.—*Subjects Studied and Number of Urobilinogen Tests*

No. of Subjects	Diagnosis	Total No. Tests	Average No. Test Per Patient
21	Acute myocardial infarction	186	9.3
9	Suspected myocardial infarction	78	7.6
20	Controls	119	5.5
7	Liver disease	34	4.8
3	Pulmonary infarction	34	10.3

pressure fell to shock levels in five, in seven there was moderate reduction in systolic and diastolic pressure without the appearance of the usual features of vascular collapse, and in nine there was no appreciable change in blood pressure. However, of this latter group, five of the patients were not admitted to the hospital until 48 hours or longer after the onset of the attack and an initial decline in blood pressure might well have been missed. Nevertheless, none of the nine patients exhibited the signs or symptoms of shock while under observation. Table 2 shows the data concerning urobilinogen excretion and the duration of positive tests in relation to the changes in blood pressure.

Five of the patients with myocardial infarction also had congestive heart failure. Three of the five were admitted in acute pulmonary edema; one with massive peripheral edema, and one with minimal signs of left heart decompensation. There was no apparent correlation between the presence of the heart failure and the appearance or duration of the increased urobilinogen excretion, although the number of patients with significant right heart failure was inadequate for proper evaluation of this factor.

The occurrence of centrilobular hepatic necrosis following fatal myocardial infarction has been demonstrated at autopsy by Clarke.[6] He reported the presence of circulatory collapse in five of the nine patients examined and attributed the hepatic necrosis to the shock. The presence of hepatic changes of this nature would provide a reasonable explanation for the occurrence of a positive urobilinogen test. How-

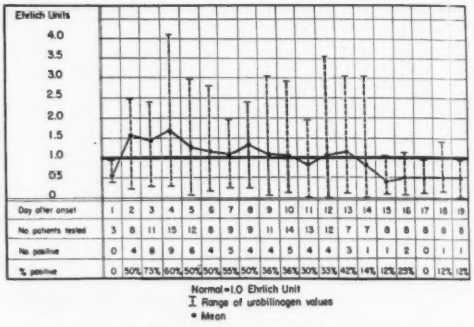

FIG. 1. The range and mean of serial urine urobilinogen excretion in 21 patients with confirmed acute myocardial infarction.

ever, in this study, 9 of 21 patients with confirmed infarction showed no appreciable drop in blood pressure, yet eight of the nine patients had increased excretion of urobilinogen. It is also apparent that urobilinogen values were normal in one patient who was in shock at admission. Of the few patients in the group subjected to the usual hepatic function tests, it was observed that there was no retention of bromsulfalein, no hyperbilirubinemia, and the cephalin flocculation and the thymol turbidity tests were within normal limits.

Another observation of interest was the appearance of a positive test during the first week of illness in three patients where the diagnostic electrocardiographic changes did not develop until the second week of hospitalization. This suggests the possible value of the urobilinogen determination in patients where the usual methods are unrewarding in the diagnosis of

myocardial infarction. It is also of note that the degree and duration of increased urobilinogen excretion had no apparent bearing on the outcome of the myocardial infarction.

Of the nine patients listed in table 3 with suspected myocardial infarction, which was not confirmed by "the necrosis or injury pattern" in the electrocardiogram, five exhibited positive urobilinogen tests. The history of the attack, the laboratory findings, the course of illness, and the electrocardiograms were reviewed in all nine patients in an attempt to confirm or disprove the diagnosis of acute myocardial infarction. It was felt that the data were consistent with the initial diagnosis in patients number 2, 4, and 6; that an acute myocardial infarction had not been sustained in patients 7 and 8; and that the diagnosis remained questionable in patients 1, 3, 5, and 9. These data are summarized in table 3.

The diagnosis of pulmonary infarction was confirmed by roentgenogram in three patients two of whom had also sustained an acute myocardial infarction. In all three patients the urine urobilinogen was markedly elevated, reaching 20 Ehrlich units in one instance. Two of the patients with pulmonary infarction were considered to be in shock at some period during the illness. In three additional instances of acute myocardial infarction, pulmonary infarction was suspected but not confirmed. However, in none of the latter patients was it observed that the urobilinogen assumed higher levels or remained positive longer than in the uncomplicated cases of myocardial infarction.

Twenty individuals were selected as controls. The group included three apparently healthy laboratory personnel and 17 patients; at least three samples were analyzed per subject and the average number of determinations was 5.5. The descriptive information concern-

TABLE 2.—*Urine Urobilinogen as Related to Fall in Blood Pressure in 21 Patients with Infarction Confirmed by Electrocardiogram*

Patient	Blood Pressure†	Urine Urobilinogen* Ehrlich Units	Duration of Positive Tests
1. A. L.		3.6 U, + on 4th day	to 19th day
2. C. S.		2.8 U, + on 2nd day	to 18th day
3. J. H.	Shock	0.9 U, negative	died 21st day
4. R. W.		2.4 U, + on 3rd day	died 9th day
5. C. C.		2.4 U, + on 6th day	to 9th day
6. E. H.		1.9 U, + on 2nd day	to 10th day
7. G. S.		1.9 U, + on 3rd day	to 3rd day
8. E. B.		4.2 U, + on 3rd day	to 5th day
9. G. F.	Moderate fall	1.2 U, + on 4th day	to 4th day
10. C. M.		2.5 U, + on 3rd day	to 13th day
11. J. G.		1.2 U, + on 5th day	to 12th day
12. E. W.		2.9 U, + on 3rd day	to 8th day
13. E. C.		1.3 U, + on 3rd day	to 3rd day
14. M. B.		1.5 U, + on 5th day	to 6th day
15. F. F.		2.2 U, + on 4th day	to 10th day
16. A. P.		1.3 U, + on 4th day	to 5th day
17. E. M.	No appreciable change	2.2 U, + on 2nd day	to 9th day
18. H. J.		3.3 U, + on 3rd day	to 16th day
19. E. K.		0.6 U, negative	
20. D. V.		1.1 U, + on 9th day	to 9th day
21. I. R.		1.6 U, + on 2nd day	to 2nd day

* Highest urobilinogen level attained and the day positive test appeared.

† Definition of blood pressure changes:

Shock: systolic pressure under 100 mm. Hg in addition to the usual manifestations of circulatory collapse.

Moderate fall: systolic pressure lower by 20 to 30 mm. Hg and diastolic pressure lower by 10 to 15 mm. Hg.

ing this control group was as follows:

Cardiovascular disease	7
Pulmonary fibrosis with emphysema heart	2
Arteriosclerotic (acute left heart failure)	1
Rheumatic (no failure)	2
Arteriosclerotic (no failure)	2
Chronic diseases	8
Cerebrovascular accident	2
Rheumatoid arthritis	6
Acute febrile illness	2
Rubella	1
Acute rheumatic fever	1
Nonhospitalized normals (laboratory personnel)	3

patient had Laennec's cirrhosis in an inactive phase of the disease.

Jones and associates[8] have investigated the occurrence of impaired liver function in patients following anesthesia. It was noted that the changes in liver function were essentially similar in comparing local anesthesia with general anesthesia. On this evidence it was suggested that the liver impairment noted was due to the stress reaction incidental to the operative procedure. It is reasonable to postulate that similar factors are operative in a patient undergoing the severe emotional and physical impact of an acute myocardial infarction. In support of the occurrence of the stress

TABLE 3.—*Pertinent Findings and Urobilinogen Excretion in Nine Patients with Suspected Myocardial Infarction*

Patient	Erythrocyte Sedimentation Rate (mm.)†	White Blood Count	History	Positive Urobilinogen	Temperature Elevation	Blood Pressure Fall	Myocardial Infarction*
1. C. W.	19	8,100	A.P., precordial pain 10 hours	10th and 11th days	3rd day only	none	questionable
2. P. H.	16	18,600	A.P., substernal pain several hours	absent	intermittent to 15th day	none	probably present
3. J. K.	50	11,800	Acute pulmonary edema	6th day only	1st and 2nd day	slight	questionable
4. J. D.	—	9,800	Two previous infarctions A.P. one week	3rd and 9th days	none	none	probably present
5. F. G.	12	9,100	Precordial pain 11 hours	absent	to 5th day	none	questionable
6. N. L.	50	10,250	Hypertension dyspnea two days	4th to 6th day	to 4th day	none	probably present
7. M. D.	—	7,500	A.P., heart failure	absent	12th to 14th day	none	absent
8. E. K.	30	6,700	A.P., heart failure	absent	none	none	absent
9. M. H.	—	4,800	Previous infarction, substernal pain two hours	2nd day only	to 4th day	none	questionable

* Diagnostic impression after review of all available information. † Wintrobe method.
A.P. = Angina Pectoris.

In this group of subjects the urine urobilinogen was elevated in only four specimens. There was one elevation to 1.4 Ehrlich units of 12 tests in a patient with a cerebrovascular accident; two elevations to 1.1 Ehrlich units of 12 tests in a patient with pulmonary fibrosis; and one elevation to 1.4 Ehrlich units of five tests in a patient with rheumatoid arthritis. In the positive control group with established liver disease all but one of the seven patients had increased urine urobilinogen, and this

reaction is the observation[9, 10] of eosinopenia during the first few days after the attack in the majority of patients sustaining myocardial infarction. With serial, daily, direct counts the level of eosinophils was found to increase gradually to normal figures. An essentially similar pattern of circulating eosinophils has been reported to occur postoperatively.[11]

SUMMARY AND CONCLUSIONS

1. Thirty selected patients with suspected acute myocardial infarction have been studied

with the serial, semiquantitative, urine urobilinogen determination. The test was positive in 19 of 21 patients in whom the diagnosis was confirmed by the electrocardiogram, and in five of nine patients in whom the "necrosis or injury" pattern was absent. Of these five patients it was felt that three had sustained myocardial infarction in the absence of diagnostic electrocardiographic changes.

2. The highest percentage of positive tests occurred on the second and third days after the attack; the majority of positive tests was confined to the eight day period after the attack.

3. There was no apparent correlation between the occurrence of elevated urine urobilinogen levels and the presence of peripheral circulatory collapse or cardiac decompensation.

4. It is postulated that the increase in urine urobilinogen is due to the impaired liver function induced by the stress reaction of the myocardial infarction.

5. The determination of urine urobilinogen may have some value in confirming the diagnosis of acute myocardial infarction in instances where other evidence is inconclusive; its value in prognosis is not apparent in this study.

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REFERENCES

[1] Watson, C. J., Schwartz, S., Sborov, V., and Bertie, E.: Studies of urobilinogen. V. A simple method for the quantitative recording of the Ehrlich reaction as carried out with urine and feces. Am. J. Clin. Path. **14:** 605, 1944.

[2] —: The pyrrol pigments with particular reference to normal and pathologic hemoglobin metabolism. In Downey's Handbook of Hematology. New York, Hoeber, 1938. Vol. IV, p. 2447.

[3] —: The bile pigments. New England J. Med. **227:** 665, 705, 1942.

[4] Brereton, H. G., and Lucia, S. P.: Quantitative method for the determination of urobilinogen in stool and of urobilinogen and bilirubin in urine. Am. J. Clin. Path. **18:** 887, 1948.

[5] Watson, C. J.: Personal communication, 1950.

[6] Clarke, W. T. W.: Centrilobular hepatic necrosis following cardiac infarction. Am. J. Path. **24:** 249, 1950.

[7] Voegtlin, W. L.: Possible source of error in quantitative determination of urobilinogen by Watson method. Am. J. Clin. Path. **18:** 84, 1948.

[8] Fairlie, C. W., Barss, T. P., French, A. B., Jones, C. M., and Beecher, H. K.: Metabolic effects of anesthesia in man. IV. A comparison of the effects of certain anesthetic agents on the normal liver. New England J. Med. **244:** 615, 1951.

[9] Evans, J. M., Wood, O. H., and Wilmer, G. M.: Unpublished observations.

[10] Ellestad, M. H., and Reed, J.: Circulating eosinophiles in cardiovascular stress. Ann. Int. Med. **36:** 551, 1952.

[11] Roche, M., Thorn, G. W., and Hills, A. G.: The levels of circulating eosinophiles and their response to ACTH in surgery. New England J. Med. **242:** 307, 1950.

CLINICAL PROGRESS

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Diagnosis and Management of Common Malformations of the Heart

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ACCURATE diagnosis and the proper management of children with malformations of the heart becomes increasingly important as more and more malformations become amenable to surgery. Even patients who cannot be helped by surgery should be encouraged to lead useful lives. In many instances it is quite as much the doctor's attitude as the malformation which makes an invalid out of the child.

Fortunately a number of malformations can be diagnosed with comparative ease by simple clinical methods, without recourse to cardiac catheterization or angiocardiography. The latter procedures are useful adjuncts, but by themselves seldom give the correct answer. Furthermore, they are not innocuous procedures; therefore they should not be used routinely, but only to obtain specific information on some particular point. The purpose of this paper is to review the common malformations of the heart which can be diagnosed clinically and to give the clinician a number of hints concerning the diagnosis and also some general principles concerning the management of these children.

I: Malformations of the Heart Which Show No Cyanosis

Patent Ductus Arteriosus

Persistent patency of the ductus arteriosus is usually a relatively easy diagnosis. The diagnosis is based on the occurrence of a continuous murmur over the pulmonary area in a person who shows no cyanosis. The murmur may vary considerably in intensity, but usually it has a systolic accentuation and the second sound is readily audible in the middle of the murmur. The electrocardiogram ordinarily shows a balanced axis or a tendency to left ventricular hypertrophy.

The x-ray commonly reveals fullness of the pulmonary conus and frequently there is evidence of slight left auricular enlargement. The size of the heart varies with the size of the ductus. In general, the larger the ductus, the larger is the heart and the more pronounced are the hilar markings. A hilar dance is, however, not common. The red blood cell count, the amount of available hemoglobin, and the hematocrit reading should be within normal limits.

The occurrence of cyanosis or polycythemia is strongly against the diagnosis of patency of the ductus arteriosus; even if there is patency of the ductus, either of these findings is almost invariably a contraindication to the surgical closure of the ductus arteriosus.

The fact that the continuous murmur seldom develops before 1 year of age and often not until the patient is 3 or 4 years of age, means that the diagnosis prior to this time is difficult. Fortunately in most instances the condition causes little or no disability. Therefore, in the vast majority of patients, early diagnosis is not necessary.

Occasionally, however, a large patent ductus arteriosus may cause great difficulty in early

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infancy.[1] Therefore an infant with great cardiac enlargement and evidence of excessive pulmonary blood flow who has a balanced electrocardiogram and has only a systolic murmur or both a systolic murmur and a mid-diastolic murmur but no continuous murmur, should be sent to a specialist for study.

When patency of the ductus arteriosus occurs as an isolated malformation, either ligation or division of the ductus arteriosus restores the heart to normal.[2, 3] Even if there is an additional malformation, provided there is no cyanosis and the oxygen saturation of the arterial blood is normal, in almost every instance closure of the ductus arteriosus lessens the strain on the heart.

The ideal age for operation is between 4 and 6 years; nevertheless, an infant or an adult in heart failure may be greatly benefited by operation.

Coarctation of the Aorta

Coarctation of the aorta is usually easy to diagnose. The diagnosis is based upon the finding of a strong pulse in the upper extremities combined with a weak or absent pulse in the lower extremities. This finding should always suggest the possibility of a coarctation of the aorta, and should lead to the search for evidence of collateral circulation. Pulsating vessels are frequently palpable in the interscapular region. The occurrence of a systolic murmur in this area which is not audible over the precordium is a relatively common finding in a coarctation of the aorta.

The most characteristic of all signs is notching of the ribs. Notching of the ribs may be seen as early as 3 years of age, but it is usually not apparent until 12 or 14 years of age. Its occurrence in adults is the rule. Indeed absence of notching of the ribs in an adult who has clinical evidence of coarctation of the aorta should always suggest the possibility of coarctation of the abdominal aorta. Under such circumstances either angiocardiography or aortography is indicated to determine the location of the constriction. If aortography is attempted, 35 per cent Diodrast should be used, as the injection of 70 per cent Diodrast directly into the aorta is an extremely dangerous procedure.

When coarctation of the aorta occurs proximal to the entrance of the ductus arteriosus, the low pressure in the descending aorta causes the blood to flow from the pulmonary artery to the descending aorta. Unless the ductus arteriosus undergoes prompt obliteration the infant may develop severe right-sided heart failure. If such an infant fails to respond to digitalis therapy, early operation is indicated.

Coarctation of the aorta may occur in combination with other anomalies. The occurrence of an additional malformation, especially that of aortic insufficiency, is usually an added indication for operation.

Coarctation of the aorta is another malformation in which operation may restore the heart and circulation to normal.[4–6] Furthermore there is strong evidence that arteriosclerotic changes begin at an earlier age in a patient with hypertension than in the normal individual. This means that operation is easier and more likely to be successful in children than in adults.

The author does not, however, believe that surgery is indicated for every patient with a coarctation of the aorta. Early operation is indicated if the child has symptoms referable to the malformation, if he has marked hypertension or if he has electrocardiographic evidence of left ventricular strain. The optimum time for operation is between 4 and 10 or 12 years of age. If, however, the patient is asymptomatic and has a normal bood pressure and the condition is picked up upon routine examination, he can well afford to wait until the surgical technic has been still further perfected.

Vascular Ring

A vascular ring which encircles the trachea and esophagus may result from the persistence of both the right and left aortic arches which unite posteriorly to form the descending aorta, or it may be formed by the combination of a right aortic arch and left descending aorta when the ductus arteriosus or a strand thereof persists in its normal position and extends from

the pulmonary artery to the descending aorta on the left side. In the majority of instances, a vascular ring occurs as an isolated anomaly.

Stridor is the outstanding symptom.[7] It is usually present from birth. Dysphagia is common and not infrequently the infant develops attacks of dyspnea during which he may become deeply cyanotic. These symptoms may be alleviated by hyperextension of the head and neck.

The combination of respiratory difficulty and difficulty in feeding, with the consequent failure to gain, render these infants very susceptible to tracheitis, bronchitis, and pneumonia.

The condition can usually be readily diagnosed by x-ray or fluoroscopic examination. The retroesophageal aorta causes marked anterior displacement of the esophagus at the level of the aortic arch. A vascular ring which results from a double aortic arch commonly causes bilateral compression of the trachea and esophagus. The diagnosis may be established by a tracheogram.[8] Delineation of the esophagus by a radio-opaque material in the lateral or oblique position usually suffices. If barium is given, the mixture should be extremely thin, because the dysphagia may precipitate an attack of dyspnea. If the infant has difficulty in swallowing, Lipiodol should be used, as aspiration of the Lipiodol does no harm.

The difficulty caused by a vascular ring can be greatly helped by operation.[9] The division of the smaller segment abolishes the ring. Such an operation should cure the condition. Unfortunately, however, the trachea may be permanently constricted or the adhesions to the surrounding tissues may be such that the division of the vascular ring does not relieve the obstruction. The improvement is greater if the tissues of the anterior mediastinum are pulled up and sutured to the sternum.[10] Even though operation is not always successful, if the baby is having attacks of dyspnea and cyanosis, operation is urgently indicated. On the other hand, when the patient is asymptomatic and the condition is picked up on routine examination, operation is not indicated.

Auricular Septal Defect and the Lutembacher Syndrome

Auricular septal defects and the Lutembacher syndrome are malformations which can be diagnosed with relative ease and accuracy. When a gross defect in the auricular septum occurs in combination with great dilatation of the pulmonary artery and congenital or acquired mitral stenosis, the condition constitutes a Lutembacher syndrome. Both malformations lead to great right-sided cardiac enlargement which frequently causes left-sided chest deformity. The patient often shows the frail build of the gracile habitus. The shunt is overwhelmingly left-to-right, and anything which increases the strain on the left side of the heart increases the volume of the shunt.

Inasmuch as the shunt is from left to right, there is no clubbing and no polycythemia; there may, however, be minimal cyanosis of the tips of the fingers and toes. The heart becomes tremendously enlarged both to the right and to the left. The apex beat is displaced down and out. A harsh basal systolic murmur with a snapping, reduplicated second sound over the pulmonary area is the rule. In addition there is usually both a systolic murmur and a low-pitched mid-diastolic murmur at the apex.

The electrocardiogram shows slight right axis deviation and widening of the QRS complex; the precordial leads generally show evidence of a right bundle branch block or the pattern of right ventricular strain.

The x-ray contour shows great right-sided cardiac enlargement and a small aortic knob; even in the presence of mitral stenosis there is seldom evidence of left auricular enlargement.[11] In cases of a Lutembacher syndrome, there is, in addition, enormous dilatation of the pulmonary artery and a conspicuous hilar dance.

These patients frequently suffer from repeated attacks of bronchitis and pneumonia. In addition they are very susceptible to rheumatic fever and to all sorts of cardiac arrhythmias. The use of prophylactic chemotherapy or antibiotics lessens the frequency of respiratory infections and rheumatic fever. Digitalis and other measures may help to control the arrhythmias.

Closure of auricular defects is being attempted but has not yet been accomplished with sufficient success and a sufficiently low mortality rate to justify operation unless the patient is suffering from severe and intractable heart failure.

Most of these patients, in spite of the great cardiac enlargement, do well. The malformation causes remarkably little difficulty during pregnancy. Therefore sterilization or interruption of pregnancy is seldom justified. In most instances, relative longevity is the rule.

Ventricular Septal Defect

Ventricular septal defect, or maladie de Roger, is the probable diagnosis in a patient with a heart of normal size and no limitation of activity, who has a harsh systolic murmur and thrill maximal in the midsternal region. The murmur radiates in all directions and may be heard posteriorly. X-ray shows the heart to be of normal size and shape. A normal electrocardiogram is the rule.

Most of these patients are asymptomatic and require no treatment except for the general prophylactic measures which are indicated for all patients with malformations of the heart (see section III).

II: Malformations Which Cause Persistent Cyanosis

Cyanosis is the bluish tinge to the skin which results from the presence of reduced hemoglobin in the circulating blood. Cyanosis may, however, be due to increased deoxygenation of the blood in the peripheral tissues; under such circumstances the oxygen saturation of the arterial blood is normal. When cyanosis is due to a venous-arterial shunt the oxygen saturation of the arterial blood is reduced. In almost every such instance the degree of oxygen unsaturation increases still further with exercise. Therefore, when in doubt concerning the occurrence or significance of cyanosis, the effect of exercise should be tested. In a patient with a venous-arterial shunt the inhalation of oxygen may increase the oxygen saturation of the arterial blood, but usually it will not raise it to normal. In contrast to this, when cyanosis is due to inability to oxygenate the blood in the lungs, as in cases of cor pulmonale, the inhalation of oxygen causes prompt disappearance of the cyanosis and the arterial oxygen saturation rises to normal.

Persistent oxygen unsaturation of the arterial blood leads to polycythemia, which renders the cyanosis more readily apparent. The low arterial oxygen saturation and the polycythemia cause clubbing of the extremities.

Broadly speaking, malformations which cause persistent cyanosis place a strain on the right side of the heart. Either the aorta arises in part or completely from the right ventricle, or the malformation places a strain on the right side of the heart of such a nature that venous blood is shunted into the systemic circulation through the foramen ovale, or there is underdevelopment of the left side of the heart as in aortic atresia or marked hypoplasia of the aorta and the systemic circulation is maintained by the right ventricle through the ductus arteriosus.

The age at which cyanosis becomes apparent offers a clue to the diagnosis. Cyanosis which is present in early infancy is generally due to the direct shunting of venous blood into the systemic circulation. The commonest malformations in this group are complete transposition of the great vessels and pulmonary stenosis or atresia. Cyanosis which becomes apparent in early childhood, that is, between 2 and 6 or 7 years of age, is usually due to a venous-arterial shunt from right auricle to left auricle through the foramen ovale. In such instances the valve of the foramen ovale has been forced open by the high pressure in the right auricle, as for example valvular pulmonary stenosis with an intact ventricular septum or Ebstein's disease. Cyanosis which develops at or shortly after puberty is usually associated with pulmonary hypertension, as for example, an Eisenmenger complex or a cor pulmonale. Pulmonary hypertension may, however, occur in infants and young children. If pulmonary hypertension occurs early or is secondary to a malformation of the left side of the heart, either the ductus arteriosus or the foramen ovale may remain patent and thereby a right-to-left shunt is established.

In malformations which cause persistent

cyanosis, x-ray and fluoroscopic findings are usually of diagnostic aid, especially as regards the size and position of the pulmonary artery and the volume of the pulmonary blood flow.

The term "pulmonary conus" has been used to connote both the "main segment of the pulmonary artery" and the "infundibular region" or the "outflow tract" of the right ventricle. The term "pulmonary conus" means the first convexity in the cardiac shadow to the left of the sternum below the shadow of the aortic knob. Recent studies with Diodrast have shown that this shadow is usually cast by the main pulmonary artery as it arises from the right ventricle. When the pulmonary artery is large and normally placed, the pulmonary conus is full. A concave curve at the base of the heart to the left of the sternum in a patient with persistent cyanosis occurs when the pulmonary artery is diminutive, absent, or misplaced.

The volume of the pulmonary blood flow can be estimated by the vascularity of the lung fields. In patients with pulmonary stenosis or atresia, the lung fields are excessively clear. In contrast to this, large blotchy shadows which radiate from the hilar regions to the lungs are indicative of large pulmonary vessels and excessive pulmonary blood flow. Pulsations in the hilar shadows vary both with the size of the pulmonary arteries and with the pressure within these vessels.

When conspicuous hilar shadows are combined with a concave curve at the base of the heart to the left of the sternum, it means a large posteriorly placed pulmonary artery, that is, a complete transposition of the great vessels and a dilated pulmonary artery. This condition may occur with two ventricles or when there is only a single ventricle.

The Tetralogy of Fallot

The tetralogy of Fallot consists of pulmonary stenosis or atresia, combined with dextroposition of the aorta, a high ventricular septal defect, and right ventricular hypertrophy. As in almost all malformations of the heart, the severity of the abnormality is subject to wide variation. Thus the pulmonary stenosis may be so extreme that the pulmonary orifice is atretic; in other instances the pulmonary stenosis is slight and the condition may be compatible with life for a number of years.

Cyanosis may be present at birth. Frequently the cyanosis does not become apparent until 3 to 6 months of age, and it may not be appreciated until the infant starts to walk. Many infants with severe degrees of pulmonary stenosis suffer from attacks of paroxysmal dyspnea which may progress to loss of consciousness. For such infants the most critical period is from 6 to 18 months of age. From 18 months to 2 years of age, the infant generally holds his own, and thereafter he starts to improve.

Clubbing develops in early childhood and becomes progressively more pronounced. The red blood cell count, the amount of available hemoglobin, and the hematocrit reading are increased. The oxygen saturation of the arterial blood is reduced and falls still further with exercise. Polycythemia increases with age. Eventually the patient is handicapped not only by the reduction of the arterial oxygen saturation but also by the increased viscosity of the blood.

The heart is but slightly if at all enlarged. A basal systolic murmur and thrill are the rule. The second sound at the base of the heart to the left of the sternum is weak or absent; it is never reduplicated. The electrocardiogram shows right axis deviation and right ventricular hypertrophy. The x-ray shows a concave curve to the left of the sternum and diminished hilar markings; the aorta may arch to the right or to the left; the pulmonary window is clear. Arm-to-tongue circulation time is short.

In a tetralogy of Fallot, the more intense the cyanosis, the greater is the patient's incapacity, and the fainter is the murmur. A very cyanotic patient may have no murmur, but if there is a minimal cyanosis and no murmur it is not a tetralogy of Fallot. There may, however, be a loud systolic murmur, minimal cyanosis, a virtually normal red blood cell count, and yet the child may suffer from a rapid drop in the arterial oxygen saturation with exercise, and consequently may be extremely incapacitated. Such children may be able to walk only a few

feet or stand only for a few minutes before they have to squat.

These children, as well as those who show cyanosis and polycythemia, can be greatly helped by operation. The optimum time for operation is between 8 and 14 years. Any operation which increases the circulation to the lungs will be of benefit. A Blalock anastomosis[12] gives excellent results, both immediate and long time.[13] A Pott's procedure[14] also gives good results.

Tricuspid Atresia

Tricuspid atresia may occur in combination with a variety of malformations. The most common of these is defective development of the right ventricle and pulmonary stenosis. This malformation closely resembles that of a tetralogy of Fallot except that the electrocardiogram shows a left axis deviation and left ventricular hypertrophy. When the tricuspid valve is atretic, the blood cannot leave the right auricle in the normal manner. It must escape through an opening in the auricular septum to the left auricle. When this opening is small and difficulty is encountered in the expulsion of blood from the right auricle, the auricular contractions are transmitted to the liver and these pulsations are palpable at its margin.

When tricuspid atresia is associated with pulmonary stenosis or atresia, the management and treatment are the same as for a tetralogy of Fallot. Nevertheless, owing to the variety of associated anomalies, operation may lead to progressive cardiac enlargement and cardiac failure. The over-all mortality rate is nearly twice as high as for a tetralogy of Fallot. Consequently only the seriously incapacitated patient should be recommended for surgery.

Pure Pulmonary Stenosis

Pure pulmonary stenosis, pulmonary valvular stenosis with an intact ventricular septum, can usually be diagnosed by simple clinical studies.[15, 16] The diagnosis is based upon the finding of a harsh systolic murmur and thrill over the pulmonary area, combined with a weak or absent pulmonic second sound and electrocardiographic evidence of a marked right axis deviation and either right ventricular hypertrophy or a right bundle branch block. The size of the heart and the degree of dyspnea vary with the severity of the pulmonary stenosis. The obstruction at the pulmonary orifice causes difficulty in the ejection of blood from the right ventricle and increases the work required of this chamber. The pressure within the right ventricle gradually rises. There results right ventricular hypertrophy.

If the pulmonary stenosis is severe, the heart becomes greatly enlarged. The pulmonary artery distal to the stenosis becomes dilated and its main branches are large and conspicuous; nevertheless the pulsations within these vessels are minimal or absent. Sooner or later the increased pressure in the right ventricle renders it difficult for the right auricle to empty itself. The right auricle undergoes dilatation and hypertrophy. Not infrequently the forceful contractions of the right auricle cause the auricular pulsations to be palpable at the margin of the liver.

The presence or absence of cyanosis depends upon whether or not the foramen ovale is completely sealed. If the foramen ovale is completely sealed, there is no cyanosis. If, however, there is probe patency of the foramen ovale, the high pressure in the right auricle will force the valve covering the foramen ovale to open and a right-to-left shunt will be established. Although cyanosis of this origin may be present at birth, it usually develops insidiously and becomes manifest between 2 and 6 years of age.

The pulmonary stenosis prevents the normal increase in the pulmonary blood flow with exercise, and thus causes dyspnea on exertion. If the stenosis is extreme, the condition leads to progressive cardiac enlargement and eventually to severe right-sided cardiac failure with edema and ascites. As long as the heart is able to compensate for the increased work demanded of it, the patient remains asymptomatic. This means that cardiac enlargement precedes symptoms. For this reason patients suspected of this abnormality should be followed carefully for evidence of increase in heart size.

If the heart is normal in size and the patient is asymptomatic and the pressure within the

right ventricle is but slightly increased, operation is not indicated. If, however, the pressure in the right ventricle is higher than the systemic pressure, or if there is evidence of progressive cardiac enlargement, operation is indicated. The occurrence of cyanosis is also an indication for operation.

Valvulotomy[17–19] relieves the pulmonary stenosis. Usually the valve is so fibrotic that cutting the valve does not cause it to become insufficient. Although the systolic murmur and thrill generally persist after operation, in most instances the cyanosis completely disappears and the oxygen saturation of the arterial blood rises to normal and the patient's exercise tolerance is greatly increased.

The Eisenmenger Complex

The Eisenmenger complex consists of dextroposition of the aorta combined with a normally placed pulmonary artery which is of normal size or greatly dilated. The dextroposition of the aorta means that there is a high ventricular septal defect.

The difficulty caused by this malformation during infancy is due to excessive pulmonary blood flow. A number of infants die of cardiac failure. Those who survive, generally improve during childhood. Cyanosis is absent until late childhood or early adult life. Thereafter there is a progressive increase in the signs and symptoms. In the late stages, hemoptyses are relatively common.

Examination of the heart shows slight cardiac enlargement. Usually there is a systolic murmur and there may be an early diastolic murmur. The x-ray shows fullness of the pulmonary conus, a prominent pulmonary artery and a hilar dance. The electrocardiogram usually shows a right axis deviation and right ventricular hypertrophy. Cardiac catheterization shows a high pressure in the right ventricle and evidence of pulmonary hypertension. The pressure in the pulmonary artery is approximately the same as that in the systemic circulation. The oxygen content of the blood in the pulmonary artery is higher than that in the right auricle and that in the right ventricle, and the oxygen saturation of the arterial blood is reduced. The malformation at the present time (1952) is not amenable to surgery.

The Taussig-Bing Malformation

The Taussig-Bing malformation[20] is a transposed aorta combined with a pulmonary artery which arises mainly from the right ventricle but partially over-rides the ventricular septum and thereby readily receives blood from both ventricles.

Patients with this malformation are cyanotic from birth; nevertheless, these infants do not suffer from paroxysmal dyspnea; children with this malformation are moderately incapacitated but seldom squat when tired.

The heart is but slightly enlarged. Usually there is a soft systolic murmur. The second sound at the base is generally accentuated and frequently reduplicated. The x-ray reveals fullness of the pulmonary conus and increased hilar shadows which frequently show expansile pulsations. The electrocardiogram shows a right axis deviation and evidence of right ventricular hypertrophy.

The findings on cardiac catheterization are closely similar to those of an Eisenmenger complex. Indeed, the oxygen saturation of the blood in the pulmonary artery is higher than that in the aorta. It is frequently possible to catheterize the aorta and pulmonary artery with equal ease. The outstanding difference between this malformation and an Eisenmenger complex is that the cyanosis dates from birth.

Patients with this malformation may be slightly benefited by the creation of an auricular septal defect. Such an operation generally increases the child's exercise tolerance but seldom causes a significant decrease in the red blood cell count, the amount of available hemoglobin, or in the hematocrit reading.

Complete Transposition of the Great Vessels

Complete transposition of the great vessels means that the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. Usually both great vessels are of normal size. The pulmonary artery, however, may be greatly dilated or it may be stenotic.

Although cyanosis may not be present at birth, it is always manifest at an early age and becomes progressively more intense. The infant breathes rapidly and may suffer from

episodes of loss of consciousness. Attacks of paroxysmal dyspnea are, however, rare.

A systolic murmur is usually audible, and a gallop rhythm frequently develops. There is engorgement of the liver and congestion in the lungs. In early infancy while the ductus remains patent, some of the oxygenated blood which is pumped from the left ventricle into the pulmonary artery flows through the ductus arteriosus to the lower extremities; hence the head and upper extremities are more cyanotic than are the feet and lower extremities.

The x-ray usually reveals that the heart is enlarged both to the right and to the left. In the anterior-posterior view the shadow cast by the great vessels is narrow and there is a concave curve at the base of the heart to the left of the sternum; in addition the vascular markings are increased and extend far into the lung fields.

The electrocardiogram usually shows right axis deviation and right ventricular hypertrophy. A left axis deviation may occur when a complete transposition of the great vessels is combined with tricuspid atresia.

The malformation usually leads to progressive cardiac enlargement with engorgement of the liver and congestion in the lungs. Death generally occurs at an early age. Occasionally a circulatory balance is established and the heart ceases to enlarge. Under such circumstances the condition may be compatible with life for a number of years.

The malformation causes marked stunting of growth. The child is usually severely incapacitated, and commonly squats when tired.

As the child grows and the diaphragm descends, the contour of the heart comes to resemble that of a tetralogy of Fallot. The x-ray, however, always reveals slight cardiac enlargement and the hilar markings are more pronounced than in a tetralogy of Fallot. Many blood vessels are viewed on end and the vascular markings extend nearly to the periphery of the lungs.

When the pulmonary artery is greatly dilated, there are large blotchy vascular shadows in both hilar regions, which upon fluoroscopy usually show expansile pulsations.

When the pulmonary artery is stenosed, the condition may be extremely difficult to differentiate from a tetralogy of Fallot unless the aorta is grossly misplaced. If the aorta arises from the normal outflow tract of the right ventricle and arches boldly to the left, the prominent arc to the left of the sternum in the region of the normal pulmonary artery combined with excessively clear lung fields seen upon x-ray or fluoroscopy, offers the clue to the correct diagnosis.

A complete transposition of the great vessels combined with pulmonary stenosis, may be helped by Dr. Blalock's double procedure:[21] systemic-pulmonary artery anastomosis and the creation of an auricular septal defect.

Truncus Arteriosus

Truncus arteriosus means that there is but a single great vessel which receives the blood from both ventricles and directs the blood to the body and to the lungs. The condition is termed a "true" truncus arteriosus when the pulmonary arteries arise directly from the base of the common trunk or when there is but a single great vessel and no remnant of the pulmonary artery is found. When, however, any remnant of the pulmonary artery is found the condition is termed a "pseudo" truncus arteriosus.

Persons with this malformation show varying degrees of cyanosis and incapacity. The cyanosis and incapacity vary inversely with the adequacy of the pulmonary blood flow. Broadly speaking, the incapacity is less than in other malformations with the corresponding degree of cyanosis. These infants seldom suffer from paroxysmal dyspnea. Many children with moderate cyanosis can walk long distances at a slow pace; they do not squat when tired.

On physical examination the distinctive findings are a continuous murmur over the lungs and persistent cyanosis. The continuous murmur is not unlike that produced by a patent ductus arteriosus; it varies considerably with respiration, and is best heard when the breath is held at the end of inspiration. The intensity of the murmur is inversely proportional to the intensity of the cyanosis. When cyanosis is minimal, the murmur is loud and is usually widely transmitted throughout the lungs both front and back. The murmur may be audible only on one side. When it is maximal

over the pulmonary area, the malformation may be mistaken for that of a patent ductus arteriosus. In contrast to the murmur of a patent ductus arteriosus, this murmur seldom produces a thrill. When a thrill is present, it is widely transmitted and is usually readily palpable in the axilla or over the back.

In most instances the murmur is not very loud and cyanosis is moderately severe. Under such circumstances the murmur is frequently confined to a relatively small area, front, back or in the axilla. The location of the murmur depends upon the location and course of the vessels of the collateral circulation. The intensity of the murmur varies with the volume of blood coursing through these vessels. When cyanosis is intense and the pulmonary blood flow is minimal, there may be no murmur.

X-ray and fluoroscopic examination are frequently of aid in diagnosis. The heart is slightly to moderately enlarged and there is absence of fullness of the pulmonary conus. The large truncus arteriosus arches either to the right or to the left at an abnormally high level. The shadows cast by the pulmonary arteries are usually replaced by fine vascular markings which radiate from the hilar regions. In addition, delineation of the esophagus with barium in one or both oblique views may reveal the presence of retroesophageal vessels; in rare instances the esophagus is caught between vessels of the collateral circulation and displaced in a bizarre manner.

When the pulmonary blood flow is relatively adequate, there is no need for operation and no benefit can be derived therefrom. When the pulmonary blood flow is markedly reduced, these patients may be greatly helped by a Blalock-Taussig operation, provided there is a rudimentary pulmonary artery which is capable of conducting blood to the lungs. Those patients in whom the operation has been successfully performed have been greatly benefited. The over-all mortality rate, however, has been 25 per cent.

Pulmonary Hypertension and Persistent Patency of the Ductus Arteriosus (Reversed Ductus)

The occurrence of pulmonary hypertension combined with persistent patency of the ductus arteriosus causes a characteristic clinical syndrome.[22, 23] The condition is frequently associated with malformations of the left side of the heart such as underdevelopment of the left ventricle, mitral stenosis, marked hypoplasia of the ascending aorta or extreme coarctation of the aorta. Whenever the pressure in the pulmonary artery is higher than that in the descending aorta, blood will flow from the pulmonary artery to the descending aorta. Consequently the feet will be more cyanotic than the hands. Frequently some blood from the pulmonary artery is forced back into the ascending aorta. Under such circumstances the left hand will be more cyanotic than the right.

The malformation places a strain on the right side of the heart. The electrocardiogram shows right axis deviation and evidence of right ventricular hypertrophy. The pulmonary valves frequently become insufficient as evidenced by a high-pitched, blowing diastolic murmur along the left sternal border. The difference in cyanosis between the upper and lower extremities offers the clue to the diagnosis. This can be confirmed by the simultaneous determination of oxygen content in the right brachial and femoral arteries. The oxygen content of the sample of blood from the right brachial artery will be normal and that from the femoral artery will be virtually the same as that of the pulmonary artery. Upon cardiac catheterization the pressure in the pulmonary artery will be elevated and it is usually possible to catheterize the descending aorta through the ductus arteriosus. Angiocardiogram will show simultaneous visualization of the descending aorta and the branches of the pulmonary artery.

Ligation of the ductus is generally contraindicated because of the extreme pulmonary hypertension and the left-sided heart lesion.

Dextrocardia without Situs Inversus and Situs Inversus with Levocardia

Dextrocardia without situs inversus and situs inversus with levocardia are usually extremely complicated malformations. A single ventricle is relatively common with dextrocardia. Anomalies of venous return are common when situs inversus is combined with levocar-

lia. Although the malformation is seldom as simple as it appears to be, patients with these anomalies who show intense cyanosis, clear lung fields, and no hilar pulsations, may be helped by surgery.

III: General Rules in Regard to Management of Patients with Malformations of the Heart

1. Do not give a hopeless prognosis. Most of these children do better than the doctor anticipates. A poor prognosis not only increases the mother's anxiety but is likely to create a serious behavior problem in the child. Generally it is wise to tell the child he has a heart murmur but not to make an issue of it.

2. Allow the child to lead as normal and as active a life as is humanly possible. We all gain strength by using it. Moreover, almost every child with a malformation of the heart limits his own activity; there is seldom need for the doctor or for the parent to do so.

3. Urge the parents not to spoil the child. Warn the parents that the child may have to ask favors from his friends. The less the child is spoiled, and the better he is liked by his fellow playmates, the happier his life will be.

4. Immunization should be given at the usual time.

5. Prophylactic penicillin or some other antibiotic should always be given prior to dental extraction or tonsillectomy. The dosage recommended by the Council on Rheumatic Fever of the American Heart Association in 1952 is as follows: 400,000 units of crystalline penicillin G one-half hour prior to extraction; for the following three days the patient should receive either a daily dose of 400,000 units of slow-acting penicillin intramuscularly, or 400,000 units of oral penicillin three times daily one-half hour before meals.

6. Education is important. Whenever possible send the child to a regular school.

7. Death may result from anoxemia or occasionally from cardiac failure, subacute bacterial endocarditis, or brain abscess; but the usual childhood diseases or the ordinary intercurrent illnesses are generally well tolerated. Common colds and even pneumonia are seldom fatal.

8. Subacute bacterial endocarditis is now a curable disease. At the present time eight weeks of intensive antibiotic therapy is recommended. Whenever possible, the diagnosis should be established before treatment is started.

9. German measles in the first trimester of pregnancy is associated with a high incidence of congenital malformations of the heart, congenital cataracts and microcephaly in the offspring. The cardiac abnormality is the least serious of these three complications. The resultant malformation is frequently a patent ductus arteriosus. Microcephaly is a terrible tragedy. The earlier the infection occurs, the greater is the risk of injury to the fetus. If the infection occurs during the first month of pregnancy, the chance of a defective offspring is nearly 100 per cent. After the third month, German measles seldom if ever injures the fetus.

10. The incidence of malformations of the heart in siblings is so low that subsequent pregnancies can be recommended.

11. Women with malformations of the heart usually tolerate pregnancy better than is anticipated. Furthermore, the number of malformations amenable to surgery is constantly increasing; therefore only under exceptional circumstances is sterilization justified.

Special Considerations for the Cyanotic Child

1. An adequate fluid intake is important in order to lessen the danger of cerebral thrombosis. An infant should receive 1000 cc. of fluid per day; a child of 2 to 8 years, 1500 cc.; a child 8 to 12 years of age, 1500 to 2000 cc. Children over 12 years should receive a minimum of 2000 cc. Many young adults take 3000 cc. or even 4000 cc. of fluid per day. No patient with a polycythemia should go more than 12 hours without fluid. In case of vomiting, diarrhea, or excessive heat, the fluid intake should be increased.

2. The treatment of paroxysmal dyspnea: (*a*) Place the infant in the knee-chest position. This may be sufficient to end the attack. (*b*) Morphine sulfate (1 mg. per 10 pounds of body weight) is nearly specific for relief of paroxysmal dyspnea. (*c*) Inhalation of oxygen may help.

3. The treatment of the acute attacks of

dyspnea and cyanosis which occur in infants with a vascular ring may be alleviated by hyperextension of the head and neck.

4. Anoxemia causes retardation in growth and development, but does not cause mental retardation. The converse is also true: improvement of the circulation to the brain does not lessen mental retardation. Furthermore, a physically strong, mentally retarded child may get into far more trouble in this world than a mentally retarded child who is severely physically incapacitated.

5. In the evaluation of the advisability of early operation for a cyanotic infant, the degree of oxygen unsaturation of the arterial blood is far more important than is the intensity of the murmur. In most instances a malformation with a loud murmur carries a better prognosis than one in which there is no murmur. Indeed, the absence of a murmur is generally indicative of an extremely serious malformation. Under such circumstances if the lung fields are excessively clear, early operation is usually indicated.

6. Almost any anesthesia is well tolerated by a cyanotic patient who suffers from reduction of pulmonary blood flow provided he receives supplementary oxygen throughout the time of the anesthesia.

In conclusion, much can be done for the child with a malformed heart. An ever increasing number of malformations of the heart can be helped by surgery. Even if it is not now possible to help the child, it may yet be possible within the life span of the patient. Therefore, it is wrong to treat the child as if he were inevitably going to be a cardiac invalid throughout his life or die at an early age. Indeed, the child should be surrounded by a healthy, happy atmosphere, and the parents reminded that many persons have lived useful and significant lives without perfect health and strength.

REFERENCES

[1] Dammann, J. F., and Sell, C. G. R.: Patent ductus arteriosus in the absence of a continuous murmur. Circulation **6:** 110, 1952.

[2] Gross, R. E., and Hubbard, J. P.: Surgical ligation of a patent ductus arteriosus—report of first successful case. J. A. M. A. **112:** 729, 1939.

[3] —, and Longino, L. A.: The patent ductus arteriosus—observations from 412 surgically treated cases. Circulation **3:** 125, 1951.

[4] Crafoord, C., and Nylin, G.: Congenital coarctation of the aorta and its surgical treatment. J. Thoracic Surg. **14:** 347, 1945.

[5] Gross, R. E.: Surgical correction for coaretation of the aorta. Surgery **18:** 673, 1945.

[6] —: Coaretation of the aorta—treatment of one hundred cases. Circulation **1:** 41, 1950.

[7] Wolman, I. J.: Syndrome of constricting double aortic arch in infancy. J. Pediat. **14:** 527, 1939

[8] Neuhauser, E. B. D.: The roentgen diagnosis of double aortic arch and other anomalies of the great vessels. Am. J. Roentgenol. **56:** 1, 1946.

[9] Gross, R. E.: Surgical relief for tracheal obstruction from a vascular ring. New England J. Med. **233:** 586, 1945.

[10] —, and Neuhauser, E. B.: Compression of the trachea or esophagus by vascular anomalies: surgical therapy in 40 cases, Pediatrics **7:** 69, 1951.

[11] Roesler, H.: Interatrial septal defect. Arch. Int. Med. **54:** 339, 1934.

[12] Blalock, A., and Taussig, H. B.: Surgical treatment of malformations of the heart. J. A. M. A. **128:** 189, 1945.

[13] Taussig, H. B., King, J. T., Bauersfeld, S. R., and Padmavati-Iyer, S.: Results of operation for pulmonary stenosis and atresia (Report of 1,000 Cases). Tr. A. Am. Physicians **64:** 67, 1951.

[14] Potts, W. J., Smith, S., and Gibson, S.: Anastomosis of aorta to pulmonary artery. J. A. M. A. **137:** 343, 1948.

[15] Engle, M. A., and Taussig, H. B.: Valvular pulmonic stenosis with intact ventricular septum and patent foramen ovale. Circulation **2:** 481, 1950.

[16] Brock, R. C., and Campbell, M.: Valvulotomy for pulmonary valvular stenosis. Brit. Heart J. **12:** 377, 1950.

[17] —: Valvulotomy for relief of congenital pulmonary stenosis. Brit. M. J. **1:** 1121, 1948.

[18] —: The surgery of pulmonary stenosis. Brit. M. J. **2:** 399, 1949.

[19] Potts, W. J., Gibson, S., and Riker, W. L.: Congenital pulmonary stenosis with intact ventricular septum. J. A. M. A. **144:** 8, 1950.

[20] Taussig, H. B., and Bing, R. J.: Complete transposition of the aorta and a levoposition of the pulmonary artery. Am. Heart J. **37:** 551, 1949.

[21] Blalock, A., and Hanlon, R. C.: The surgical treatment of complete transposition of aorta and pulmonary artery. Surg., Gynec. & Obst. **90:** 1, 1950.

[22] Dammann, J. F., Berthrong, M., and Bing, R. J.: Reverse ductus: A presentation of the syndrome of patency of the ductus arteriosus, with pulmonary hypertension and a shunting of blood flow from pulmonary artery to aorta. (In preparation.)

[23] Taussig, H. B., Bauersfeld, S. R., and MacDonald, A. J.: Pulmonary hypertension and persistent patency of the ductus arteriosus. Preliminary report presented at the American Pediatric Society Meeting (May 1952); abstract to be published in Pediatrics (now in press).

ABSTRACTS

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BLOOD COAGULATION

Macht, D. I., and Golden M. R.: Influence of Amphetamine On Blood Coagulation. Arch. internat. de pharmacodyn. et de thérap. **89:** (Jan.), 1952.

Amphetamine in doses of 5 mg. or more, administered by stomach and also by parenteral injection in rabbits and dogs, accelerates clotting time of whole blood as studied by the Lee and White method. Similar results were obtained in a series of human subjects to whom the drug was administered by mouth. Methylamphetamine and dextroamphetamine act similarly but to a lesser degree than amphetamine itself.

BERNSTEIN

Douglas, A. S., and Brown, A.: Effect of Vitamin-K Preparations on Hypoprothrombinaemia Induced by Dicoumarol and Tromexan. Brit. M. J. **4755:** 412 (Feb.), 1952.

The effect of certain substances with vitamin K activity in modifying the action of dicumarol and Tromexan has been investigated in the human subject. The vitamin K preparations employed were vitamin K_1, Menaphthone, Acetomenaphthone, Kapilon, Synkavit, and water-soluble K analogue (Boots).

Apart from vitamin K_1, these substances have been shown to possess a minor and inconstant ability to modify the action of these anticoagulants. Vitamin K_1, on the other hand, is a reliable and efficient antidote, and is capable of completely blocking the action of therapeutic doses of dicumarol and Tromexan, and capable of restoring to safe levels within a few hours excessive hypoprothrombinaemia due to these drugs.

Since these differences between the vitamin K preparations are not merely a question of dosage, of all the substances tested here only vitamin K_1 can be regarded as a reliable antidote for a hypoprothrombinaemic emergency.

BERNSTEIN

CONGENITAL ANOMALIES

Shumacker, H. B., Jr.: The Diagnosis of Coarctation of the Aorta with Particular Reference to the Importance of Absent or Diminished Abdominal Aortic Pulsation. Ann. Surg. **135:** 111 (Jan.), 1952.

The author calls attention to the fact that absence or diminution of the abdominal aortic pulse is a characteristic feature of coarctation of the aorta. This sign is readily ascertained through careful inspection and palpation of the aorta. It is especially important in differentiating coarctation of the aorta from thrombosis of the bifurcation of this vessel. In the latter condition there are forceful pulsations in the proximal portion of the abdominal aorta.

ABRAMSON

Donzelot, E., Metianu, C., and Durand, M.: Right Ventricular Hypertrophy in Congenital Heart Disease. (A Physiopathologic Classification.) Arch. Mal. coeur **45:** 97 (Feb.), 1952.

The authors describe three electrocardiographic types associated with right ventricular hypertrophy due to congenital heart disease. The first termed "adaptation type" shows moderate or no axis shift in the limb leads; inversion of the T wave may be present in lead III; there is an upright QRS with or without T inversion to be found over the right precordium, but usually extending not farther than

to lead V_1. This pattern develops early in childhood and remains unaltered for years. It is found in cases in which the aorta originates partly or completely from the right ventricle.

The second pattern, called the "resistance type," shows marked right axis shift and inversion of the T wave in both leads II and III, and upright QRS complexes, depressed S-T segments and inverted T waves are seen over the whole precordium, sometimes extending up to V_6. Such an electrocardiogram is found frequently in pure pulmonary stenosis, or in association of the latter with an interatrial septal defect.

The third type of electrocardiogram, consisting of right bundle branch block, is termed by the authors the "strain type" and is found most frequently in cases with an atrial septal defect. The appearance of three different patterns of right ventricular hypertrophy in congenital heart disease can be explained on the basis of the different dynamics associated with the various lesions.

PICK

De Soldati, L., Navarro Viola, R., and Mejia, R. H.: The Ballistocardiogram in some Valvular Deformities and Cardiac Congenital Anomalies. Rev. argent. cardiol. **18:** 189, 1951.

The ballistocardiograms of 22 patients were studied. Ten cases presented mitral stenosis; one, mitral stenosis and insufficiency; two, mitral stenosis and aortic regurgitation; two, aortic insufficiency; one, subaortic stenosis and aortic regurgitation; four, coarctation of the aorta; one, patent ductus arteriosus; and one, Lutembacher's syndrome.

The tracings obtained from the patients presenting mitral stenosis showed a diphasic H wave, and often a high L and a deep M wave in 12 instances. Of the five patients in which aortic regurgitation was present, three had high ballistocardiographic waves, while the other two (those having combined mitral and aortic lesions) had a normal amplitude of the waves. In the four cases presenting coarctation of the aorta, a deep I and a shortened K wave were noted. Nonspecific modifications were noted in the case presenting Lutembacher's syndrome and in that with patent ductus arteriosus.

LUISADA

Puigbo', J. J., Moura Campos, C., Dornbecker, N., and Cahen, P.: Angiocardiography in Diagnosis of Interatrial Shunts. Arch. Inst. cardiol. Mexico **21:** 494 (Aug.), 1951.

The authors studied 15 cases of interauricular septal defects, either pure or associated with congenital or acquired lesions. All of these cases were proved by autopsy or hemodynamic studies.

Simultaneous filling of all cardiac chambers or of both auricles, and refilling of the right auricle at the time of filling of the left, are considered diagnostic data upon angiocardiography. These data were present in 93.4 per cent of the cases.

LUISADA

Limon Lason, R., Rubio, V., Rodriguez, H., Espino, J., and Novelo, S.: Association of Coarctation of the Aorta with Isolated Biventricular Aorta. Arch. Inst. cardiol. Mexico **21:** 469 (Aug.), 1951.

Cardiac catheterization proved the association of two congenital abnormalities in a 4 year old boy having a loud systolic murmur. One of them was coarctation of the aorta; the other was an overriding aorta without pulmonary stenosis (Eisenmenger complex). This resulted in severe pulmonary hypertension which was increased by the aortic obstruction.

The arterial pressure was 160/109 (76/66 in the poststenotic section of the aorta); the pulmonary arterial pressure was 160/107.

Lowering of left ventricular pressure following aortic surgery was expected also to decrease right ventricular pressure.

LUISADA

Wenger, R., and Wick, E.: Vectorcardiographic Studies in Congenital Anomalies of the Heart and Large Vessels. Cardiologia **20:** 1 (Fasc. 1), 1952.

In 54 cases with various types of congenital heart disease, all diagnosed with the help of cardiac catheterization and/or angiocardiography, and some of them verified by autopsy, vectorcardiograms were recorded in three planes. Although there was a great variability of the loop patterns, some changes appeared to be characteristic for certain groups of anomalies or for specific lesions. Thus, it was found that in the majority of Fallot's tetralogy with marked right ventricular hypertrophy, the frontal vector loop developed in a clockwise direction; while in cases with left ventricular hypertrophy, like intraventricular septal defects, tricuspid atresia and coarctation of the aorta, the frontal loop took a counterclockwise course (from right to left). However, while in septal defects and coarctation, horizontal and frontal loops had the same direction of development, in tricuspid atresia the loop viewed in the horizontal plane developed from left to right. In one case of common ventricle with other associated anomalies, the vector loop had an unusual contour in all three planes, which suggested an anomalous course of the conduction system. In general, however, spatial vectorcardiograms as found in congenital heart disease can be explained without the assumption of anomalies of intraventricular conduction.

PICK

Coelho, E., Da Fonseca, M., Pinto, R., and Nunes, A.: Pulmonary Stenosis with Interatrial Septal

Defect and Severe Cyanosis. Cardiologia **18:** 183, 1951.

Two cases of pulmonic stenosis with auricular septal defect are described. The diagnosis was made by clinical and roentgenological data, as well as by angiocardiography and catheterization, and was confirmed by postmortem findings. The differential diagnosis of the Eisenmenger complex and the tetralogy of Fallot is discussed. This is considered important because pulmonic stenosis plus interatrial septal defect does not profit by the Blalock-Taussig operation, while it does from the Brock operation (pulmonary valvulotomy).

The most significant data are prominent pulmonary arch with decreased pulmonary circulation; simultaneous filling of the two atria, the left ventricle, and the aorta two to three seconds after the injection; hypertrophy of the right ventricle; and penetration of the catheter into the left atrium.

LUISADA

Doliopoulos, T., and Maillet, J.: Levocardia with Inversion of the Abdominal Viscera and Presentation of Five Personal Observations. Cardiologia **20:** 80 (Fasc. 2), 1952.

The authors collected from the literature 34 reports on levocardia in situs inversus and added five of their own observations, two of which were verified by autopsy. Association with other congenital malformations of the heart is very common. Most frequently there is a transposition of the auricles and/or dextroposition of the aorta; in a great number of cases, atresia or hypoplasia of the pulmonary artery was found, or anomalies of the venous return to the heart. A patent ductus arteriosus was present in about half of the reported cases. These associated anomalies produce a variety of clinical symptoms, of which cyanosis, encountered in 95 per cent of the cases, seems to be the most important. The electrocardiogram is of particular interest, since in some verified cases with transposed auricles, the P wave was upright in lead I; thus the most important electrocardiographic criterion of dextrocardia was absent. A search for situs inversus (palpation of the liver and radiologic determination of the gas bubble of the stomach) should be part of the examination in every case of congenital malformation of the heart.

PICK

Dotter, C. T., and Steinberg, I.: Angiocardiography in Congenital Heart Disease. Am. J. Med. **12:** 219 (Feb.), 1952.

The indications, value, and interpretation of angiocardiography in the diagnosis of congenital heart diseases are succinctly described. Since at least 26 deaths are known to have followed angiocardiography, and the hazard of the procedure is highest in young patients with congenital heart disease, care should be exercised in the selection of cases for examination.

The authors use frontal and lateral projections routinely in the study of cyanotic congenital cardiac patients. Their cumulative experience totals about 2000 consecutive angiocardiographic examinations without a fatality. Angiocardiography, although frequently employed, is rarely necessary or indicated in the study of a variety of noncyanotic congenital cardiac lesions, such as patent ductus arteriosus and isolated septal defects. It is essential in a few noncyanotic congenital heart conditions, such as coarctation of the aorta where it provides precise anatomic information concerning the lesion.

The authors strongly recommend that all patients with cyanotic congenital heart disease be studied by angiocardiography if surgery is planned. A knowledge of normal anatomy and physiology coupled with respect for an understanding of pertinent clinical and laboratory data will greatly facilitate the interpretation of angiocardiograms. Representative angiocardiograms are reproduced and discussed.

HARRIS

Ordway, N. K.: Studies in Congenital Cardiovascular Disease. IV. Impaired Pulmonary Diffusion of Oxygen in Persons with Left-to-right Shunts. Yale J. Biol. & Med. **24:** 292 (Feb.), 1952.

Impaired pulmonary diffusion of oxygen was demonstrated in 11 out of 62 patients with left-to-right shunts. In some cases diffusion was normal at rest, but was impaired during exercise. Impairment was demonstrated by showing abnormally great differences between arterial oxygen saturations while breathing air and while breathing 100 per cent oxygen. In those who also had a right-to-left shunt the saturation during breathing 100 per cent oxygen did not reach 100 per cent, as it did in those with only a left-to-right shunt.

The author explains this finding on the basis of great augmentation of pulmonary capillary flow. In persons with large left-to-right shunts it is necessary for several times the normal amount of blood to flow through pulmonary capillaries in a given time as in the normal state. This is accomplished by dilatation of the capillary bed and increased linear velocity of blood flow. During exercise there is even greater increase in these changes. As a result there is a functional barrier to the complete transfer of oxygen from the alveolus to the blood stream, since there is insufficient exposure time for the erythrocytes in the stream. Administration of 100 per cent oxygen increases the partial pressure of oxygen in the alveoli and tends to overcome the fault.

In view of the facts that right-to-left shunts may occur without cyanosis, that cyanosis may occur without a right-to-left shunt, and that the intensity of cyanosis is not entirely dependent upon arterial anoxemia, the author offers a revision of Abbott's classification of congenital heart disease. The au-

thor's classification is based chiefly on observations made during the breathing of air and of 100 per cent oxygen:

Group 1. No shunt
Group 2. Left-to-right shunt only
  a. Normal pulmonary diffusion of oxygen
  b. Impaired pulmonary diffusion of oxygen
Group 3. Right-to-left shunt, with or without concomitant left-to-right shunt
  a. Normal pulmonary diffusion of oxygen
  b. Impaired pulmonary diffusion of oxygen

ENSELBERG

CONGESTIVE HEART FAILURE

Franco, A., and Marques, M. G.: Massive or Fractional Digitalization in Chronic Congestive Failure with Auricular Fibrillation. Cardiologia **20:** 257 (Fasc. 5), 1952.

In 20 cases with auricular fibrillation of various etiologies and chronic congestive failure, different methods of treatment with Lanatoside C (Cedilanid) were studied and compared. In 17 instances full compensation was achieved as evidenced by clinical signs and normalization of venous pressure and circulation time.

In comparing the various methods of administration of the preparation, it was found that rapid digitalization by massive intravenous doses precipitates signs of intoxication which disappear 24 hours after termination of treatment. The same is true with rapid oral digitalization. Contrary to it, signs of intoxication are minimal or absent if digitalization is carried out slowly by the oral route, or more rapidly by divided intravenous doses. As methods of choice the author recommends the following plans: For oral digitalization, 3 mg. Cedilanid the first day, 2.5 mg. the second day, followed by doses of 2 mg., 1.5 mg. and 1.0 mg., the latter continued; for intravenous digitalization, an initial dose of 0.8 mg. followed in four-hour intervals by 0.4 mg., or, in less urgent cases, in 24 and 48 hours by 0.4 and 0.2 mg.

Owing to its great therapeutic range and the rarity and transient character of its toxic effects, Cedilanid is especially indicated in cases in which prolonged digitalization is necessary and frequent medical control impossible.

PICK

McLester, J. S., and Holley, H. L.: Salt Depletion Syndrome with Increasing Edema Occurring During Mercurial Diuretic Therapy. Ann. Int. Med. **36:** 562 (Feb.), 1952.

Intensive mercurial diuresis in three patients with congestive failure was followed by an aggravation of the edematous state and the development of azotemia. These untoward reactions were promptly relieved by the intravenous administration of hypertonic salt solution. These adverse sequelae to the mercurial diuretics in these cases are ascribed to increased viscosity of the blood with resultant impairment of glomerular function, and to a paradoxic shift of sodium chloride from the extracellular fluid compartment into the cells.

WENDKOS

Axelrod, D. R., and Pitts, R. F.: The Relationship of Plasma pH and Anion Pattern to Mercurial Diuresis. J. Clin. Investigation. **31:** 171 (Feb.), 1952.

The authors studied the potentiation of mercurial diuretics by ammonium chloride in normal dogs. This potentiation is not the result of increased acidity of the urine and body fluids induced by the acidifying salt. The more significant finding is an alteration in anion pattern of the body fluids, particularly a substitution of chloride for bicarbonate. After Salyrgan, the excretion of chloride regularly exceeds that of sodium, and there is frequently a fall in plasma chloride with a rise in plasma bicarbonate.

The authors suggest that mercurial diuretics specifically block chloride absorption, and the effect of ammonium chloride on diuretics is a consequence of the hyperchloremia which is induced.

WAIFE

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Glushien, A. S., Reiter, M. D., and Fischer, H.: Coronary Embolism (Intravitam Diagnosis) and Necrotizing Renal Papillitis. Ann. Int. Med. **36:** 679 (Feb.), 1952.

A 24 year old diabetic male was admitted to the hospital with the typical clinical picture of sepsis associated with loud systolic precordial murmurs. Blood cultures yielded numerous colonies of *Staphylococcus aureus hemolyticus*. A diagnosis of acute bacterial endocarditis due to this organism was therefore made. Subsequently, because of evidences of cardiac irregularity and cardiac failure, serial electrocardiograms were made, and the findings in these cardiograms established the presence of a recent posterior wall myocardial infarction. It was therefore supposed that the infarct was the result of a septic embolus to the right coronary artery.

At autopsy, this suspicion was confirmed. On the aortic valve cusp overlying the right coronary orifice, there was a large fungating vegetation which apparently had extended upward into the aorta and from which an embolus had lodged within the right coronary artery, 6 mm. from its origin. This embolus within the right coronary artery was obviously

a purulent embolus. Distal to this occluded coronary artery, the lumen was normal. Fully half of the posterior portion of the interventricular septum was comprised of patchy, yellow-white areas, some with dark red borders and all being fairly firm. These were recognized to be myocardial infarctions. Associated, but unsuspected, was the finding of renal lesions which were characteristic of a necrotizing renal papillitis. The renal lesion was not considered to be related to the bacterial endocarditis, but it was believed to be due to the diabetic state.

WENDKOS

Carral, R., and Orizaga, M.: Luetic Aortitis. Descending Myocarditis. Arch. Inst. cardiol. Mexico **21**: 435 (Aug.), 1951.

One hundred cases of cardiovascular lues, 13.4 per cent of the autopsy reports examined, were studied. Twenty-one cases had a descending myocarditis, that is, a luetic myocarditis transmitted by contiguity from the aorta.

The clinical diagnosis of this type of myocarditis is considered difficult. The best diagnostic sign seems to be incomplete left bundle branch block in a luetic patient without aortic regurgitation. Protracted heart failure was constant, irrespective of aortic regurgitation or coronary insufficiency.

LUISADA

Hegglin, R.: The Definition of Myocardosis. Cardiologia **20**: 53 (Fasc. 1), 1952.

The term "myocardosis" was originally introduced by Wuhrmann to designate certain degenerative changes of the myocardium associated with dysproteinemia of various etiology, especially those found in liver disease. However, similar histologic changes—edema, sarcolysis and destruction of myocardial fibers, and widening and fatty infiltration of the interstitial spaces of the myocardium—are also found in other conditions which are not associated with disturbance of the protein metabolism, for example in various intoxications; on the other hand, these changes may be absent in cases with severe dysproteinemia, as in multiple myeloma and in the nephrotic syndrome.

The author suggests use of the term "myocardosis" more widely to designate generally degenerative changes of the myocardium instead of restricting this name to alterations found in one specific condition. A series of cardiologic disorders known under specific terms like the "heart in hyperthyroidism and myxedema," the "beri-beri heart," the "heart in amyloidosis," the "heart in Van Gierke's disease" and "changes occurring with derangement of the electrolyte balance" could be covered by a common name "myocardosis." Thus the whole group of degenerative alterations of the myocardium could be put in sharp contrast to changes due to inflammation (myocarditis), and to changes on a vascular basis ("myocardiosclerosis").

PICK

Di Ielsi, A. J., Pinsky, H. A., and Eynon, H. K.: Auricular Infarction: Report of Two Cases. Ann. Int. Med. **36**: 640 (Feb.), 1952.

The first of these cases was a 67 year old white male who was originally admitted to the hospital with the clinical syndrome of acute myocardial infarction. This diagnosis, however, was not clearly substantiated by the electrocardiogram. He developed further respiratory distress and the clinical features of an acute pulmonary embolism. He developed difficulty in swallowing. The x-ray examination of the chest indicated the presence of enlargement of the right side of the heart, and it was suspected, therefore, that he had dilatation of the right atrium with eventual compression of the esophagus. At necropsy, these suspicions were confirmed; and it was found that in addition to marked dilatation of the right atrium, there were many small aneurysms of the right atrium and that there were many clots filling these aneurysms. Examination of the lungs indicated the presence of multiple pulmonary emboli which obviously had their origin in the atrial thrombi. The ventricle, although scarred and fatty, was not infarcted.

The second case was that of a 69 year old white male who was admitted with the typical clinical features of acute myocardial infarction. The diagnosis was confirmed by an electrocardiogram which revealed typical changes of a recent posterior wall infarct involving the left ventricle. In addition, there were elevations of the P-Q interval in leads II and III, and for this reason an associated infarct of the atrium was suspected. At necropsy, these suspicions were confirmed.

It is because of the rarity of atrial infarction and because the electrocardiographic features of the lesion are not yet sufficiently appreciated that the authors have reported the details of these two cases.

WENDKOS

De Soldati, L., Mejia, R. H., and Navarro-Viola, R.: The Ballistocardiogram in Patients with Coronary Heart Disease. Rev. argent. cardiol. **18**: 153, 1951.

The authors present ballistocardiograms recorded in 24 patients suffering from coronary heart disease. Only five of these patients had electrocardiographic evidence of myocardial infarction, while 10 suffered from hypertension. An abnormal ballistocardiogram resulted in every case, ranging from grade 3 to grade 4 of Brown's classification. The authors stress the practical value of ballistocardiography in order to detect the presence of coronary heart disease, where other methods, including Master's two-step test, have failed.

LUISADA

Taymor, R. C., Pordy, L., Chesky, K., Moser, M., and Master, A. M.: The Ballistocardiogram in Coronary Artery Disease. J. A. M. A. **148:** 419 (Feb. 9), 1952.

Ballistocardiographic findings in 195 cases are presented and correlated with results of the Master two-step exercise electrocardiogram. Twenty-seven patients of 113 with negative two-step electrocardiographic tests had abnormal ballistocardiograms either at rest or after standard exercise. Seventy of 75 with positive two-step tests had abnormal ballistocardiograms, and six out of seven with borderline two-step tests had abnormal records.

The authors point out that the character of the ballistocardiographic waves depends on velocity and force of cardiac ejection, and has no direct correlation with the results of electrocardiography. Pathologic changes in the conduction pathways or in the myocardium itself may produce changes in the electrocardiogram. However, the mechanical function may be sufficiently impaired to produce changes in the ballistocardiogram without enough disturbance to alter the electrocardiogram. In a small percentage of patients with definite evidence of coronary artery disease in this series, the ballistocardiogram remained normal.

Further study of these cases is required to determine whether or not the finding has any prognostic value. Similar further study in the group of patients with negative electrocardiographic findings and abnormal ballistocardiograms is necessary before the complete significance of the findings is understood. The authors feel the ballistocardiogram is a useful tool in the diagnosis of coronary artery disease but should be used in conjunction with careful history, physical examination, and electrocardiographic study. The test should be recorded after standard exercise if the resting record is normal because cardiac ejection force may be impaired only after exertion.

KITCHELL

De Soldati, L., Navarro-Viola, R., and Mejia, R. H.: The Electromagnetic Ballistocardiogram in Normal Subjects and in Coronary Disease. Arch. mal. coeur **45:** 108 (Feb.), 1952.

The authors analyzed tracings obtained with Dock's ballistocardiograph in 36 normal persons of various age and in 24 patients with coronary disease. In the normal cases the magnitude of the various ballistocardiographic deflections was measured as recorded during apnea, in deep inspiration and expiration, and following exercise. The results were studied from a statistical point of view and the normal limits for the various deflections were determined.

Of the 25 cases with coronary disease, five suffered from angina following myocardial infarction, 17 had anginal pain without evidence of myocardial infarction, and three had electrocardiographic evidence of coronary disease without clinical symptoms. The ballistocardiogram was abnormal in all of them. The alterations became more marked following an exercise tolerance test, regardless of the presence or absence of electrocardiographic changes. The ballistocardiogram, therefore, appears to be of definite value for the diagnosis of coronary disease.

PICK

Robinson, J. W.: Coronary Thrombosis in Diabetes-Mellitus. An Analysis of 54 Cases. New England J.Med. **246:** 332 (Feb. 1), 1952.

This report is concerned with 54 consecutive cases of coronary thrombosis with or without myocardial infarction occurring in 52 diabetic patients observed at the Pennsylvania Hospital over an interval of six and one-half years. In this series 64.8 per cent of the patients were women in contrast to a female incidence of 21.2 per cent in a large group of nondiabetic patients observed at the same hospital during the same period. The over-all mortality was 40.8 per cent. The mortality was higher in women, in those patients who had previous coronary thrombosis, and in those whose diabetes had been inadequately controlled. The statistics accumulated in this study suggested that a diabetic man is 1.3 times as likely as his nondiabetic neighbor to suffer coronary thrombosis, whereas in a woman the possibility of coronary thrombosis is increased 14 times if she is diabetic. In this series one in five women with coronary thrombosis was also a diabetic. The role of obesity and various unknown hormonal factors in the shift of the sex incidence of coronary artery disease in diabetics is given some consideration by the author.

ROSENBAUM

Mendelson, C. L.: Coronary Artery Disease in Pregnancy. Am. J. Obst. & Gynec. **63:** 381 (Feb.) 1952.

The problem of coronary artery disease in pregnancy occurred in four patients in the author's series. In addition, 21 cases are summarized from the literature and the general management of these patients is discussed. The total mortality for the 25 patients, who ranged from 19 to 45 years of age, was 24 per cent.

Probable myocardial infarctions were recorded in 15 patients: three occurred prior to pregnancy, ten during the antepartum period, one occurred intrapartum and one postpartum. The latter two died and two infarctions were fatal during the antepartum course; two other patients died among the group of 10 without infarction but with angina syndrome due to coronary insufficiency. Some of the earlier cases were inadequately studied and may represent errors in diagnosis. It was found that once an infarct has healed, the hypervolemia associated with pregnancy was not a serious problem.

Coronary artery disease should not be consid

ered as an indication for interruption of pregnancy or for cesarean section. Nor is coronary artery disease a contraindication to these surgical procedures where other obstetric indications are present. One of the author's patients was treated for two months during pregnancy with dicumarol for a coronary occlusion. The prothrombin time was maintained at approximately twice normal. The treatment was satisfactory and a normal child was born.

SHUMAN

Freis, E. D., Schnaper, H. W., Johnson, R. L., and Schreiner, G. E.: Hemodynamic Alterations in Acute Myocardial Infarction. I. Cardiac Output, Mean Arterial Pressure, Total Peripheral Resistance, "Central" and Total Blood Volumes, Venous Pressure and Average Circulation Time. J. Clin. Investigation. **31:** 131 (Feb.), 1952.

Determining cardiac output by the dye injection method of Hamilton, the authors studied 11 patients with acute myocardial infarction, seven normal male subjects, and five hypertensive patients. Special modifications in the usual technique were made so as not to disturb unduly these acutely ill subjects. It was found that hemodynamic changes varied with the clinical state of the patient. The mean cardiac index was about 4 liters per minute in the normal young subject; 3.2 in the hypertensives who were more comparable in age to the patients with myocardial infarction; in those who showed little or no evidence of shock or congestive failure following infarction the cardiac index was about 3.4 liters per minute; in those whose illness was moderately severe, 2.9 liters per minute; and in the group suffering from cardiogenic "shock," all of whom were severely ill with extreme prostration and with the clinical appearance of shock, the mean cardiac index was 1.8 liters per minute. In general the heart rate increased with increasing severity of the infarction. The mean femoral pressure varied from 95 mm. Hg to 79 in the three groups of infarctions. Extreme hypotension was not observed in these subjects, even in those who appeared clinically to be in "shock" and who later died. There was a significant reduction in stroke volume paralleling the three groups of infarction clinically. Thus, those who were in the mild group had a stroke volume of about 76 cc. It was 50 cc. in the moderately severe group, and only 27 cc. in those who had "shock." Similarly, the total peripheral resistance was strikingly increased in the cardiogenic shock cases.

In short, in severe myocardial infarction there was a reduction of cardiac output, especially stroke volume, an increase in heart rate, total peripheral resistance, central venous pressure, and average circulation time. The less severe cases did not show these abnormalities.

The authors suggest the following sequence of events after severe myocardial infarction: A diminished contractility and a failure in stroke output. The consequent reduction of arterial pressure immediately, resulting in the activation of neurogenic reflexes and possibly other compensatory mechanisms, produces an increase in total peripheral resistance and tachycardia. This intense vasoconstriction in the presence of reduced stroke volume may be followed by a fluid retention syndrome which may result in congestive heart failure as well as shock-like state. Although these compensatory mechanisms aid in maintaining aortic pressure and hence coronary blood flow, they also may have harmful consequences by adding extra burdens to an already damaged heart. Thus, an elevated total peripheral resistance increases the work of the heart; tachycardia also adds to cardiac work and results in a less effective stroke output; and venoconstriction results in increased venous filling pressure in the presence of a failing heart.

WAIFE

Feldman, D., Silverberg, C., Birenbaum, A., and Jick, S.: Changes in the Circulating Blood Eosinophils following Acute Myocardial Infarction. Am. J. M. Sc. **223:** 168 (Feb.), 1952.

A total of 51 consecutive patients admitted to the hospital with a diagnosis of probable myocardial infarction were studied to determine the response of the fasting eosinophil count to their disease and to note whether the occurrence of secondary falls in eosinophil counts would aid in the early detection of complications. The patients were later classified into two groups: group 1, those with definite acute myocardial infarction (23 cases); group 2, included angina pectoris, pulmonary edema, probable myocardial infarction, heart falure, and chest pain (28 cases). Eosinophil counts were made on venous blood by Randolph's method using a value of 50 or more per cubic millimeter as normal.

Patients with acute myocardial infarction usually, but not invariably, had an early eosinopenia. The lack of an eosinophil fall in infarction patients who had uncomplicated recoveries was probably not on the basis of an inadequate adrenocortical response to stress, although hormonal studies were not made. It was found that acute pulmonary edema was associated with extreme eosinopenia. The eosinophil response did not aid in the prognostic evaluation of the cases, nor did it appear to be of importance in determining the presence of complications, inasmuch as wide fluctuations were noted in the absence of any apparent clinical cause.

SHUMAN

ELECTROCARDIOGRAPHY

Tartulier, M., Touriniaire, A., Deyrieux, F., and Farre, R.: A Clinical and Electrocardiographic Study in 9 Cases of Acute Cor Pulmonale. Arch. mal. coeur **45:** 120 (Feb.), 1952.

The authors present data on nine observations of

acute cor pulmonale, in two of which massive pulmonary embolism was proved by autopsy. In addition to the typical clinical symtomatology, the venous pressure was elevated during the initial stages of the accident, and subsided in the next few days. X-ray examination revealed that because of acute right heart strain, the heart shadow became more horizontal and enlarged in its transverse diameter and the pulmonary vascular markings more prominent.

The characteristic electrocardiographic pattern of McGinn and White was found in seven cases in whom a tracing was obtained within 24 hours following the episode. Within the next days the right axis deviation of QRS and the left axis shift of the T wave showed a tendency to regression towards normal. S-T deviations and T inversions in the right-sided chest leads became more pronounced in later stages of acute cor pulmonale.

PICK

Moniz de Bettencourt, J., and Baretto Fragoso, J. C.: The Electrocardiogram in Pregnancy. Acta cardiol. **7**: 123 (Fasc. 2), 1952.

In order to amplify previous observations made with the three standard leads, the authors used unipolar leads in a study of changes of the electrocardiogram produced by pregnancy. Deviation of the electrical axis to the left found in the majority of cases is usually due to horizontal position of the heart in association with elevation of the diaphragm. In some cases, however, the axis shift was to the right, and this was to a greater degree during pregnancy than in controls after delivery. This is ascribed by the authors to alterations in transmission of potentials to the left leg, caused by the pregnant uterus. The appearance of an isolated Q in lead III they explain by "vertical position of the heart with rotation to the right along the longitudinal axis, and projection of the apex in forward direction." Q_3 associated with an inverted T_3 was seen in hearts with the same rotation, but in more intermediate position. In three instances, there was an inversion of the T wave in the precordial leads, and in one instance an abnormal spatial position of the ventricular gradient. Such findings suggest that, apart from positional changes, some other "functional" factors may modify the electrocardiogram during normal pregnancy.

PICK

Bengtson, E., and Johnson, T.: Electrocardiographic Changes in Acute Anterior Poliomyelitis. Cardiologia **20**: 65 (Fasc. 2), 1952.

Two hundred consecutive cases of acute poliomyelitis were followed by serial electrocardiograms taken at about 10-day intervals. Definite alterations were found in 11.5 per cent; and when divided in age groups, in 4.2 per cent of 72 children, and 15.6 per cent of 128 adults. The changes consisted in abnormalities of the T wave and occasionally in disturbance of rhythm (A-V block, and auricular fibrillation and flutter). They were found frequently in association with abnormal clinical findings (persistent tachycardia) or subjective cardiac sensations, and in cases with involvement of the bulbar nuclei. The majority of the changes appeared in the first to second week of the disease and persisted about one month, sometimes six months to a year. In some cases the associated symptoms suggested a neurovegetative disturbance with increase of the sympathetic tone. This could be proved in several instances by the results of amyl nitrite and dihydroergotamine tests.

PICK

Gigli, G., and Scotti, G.: A Singular Electrocardiographic Tracing in a Case of Chronic Cor Pulmonale. Acta cardiol. **7**: 207 (Fasc. 2), 1952.

In a patient with clinical signs of chronic cor pulmonale, the following unusual electrocardiographic pattern was recorded: small r's in lead I; deep QS waves in leads II and III; upright T waves in all three limb leads; aV_R and aV_L were similar in contour, showing a small upright QRS and inverted T wave, while aV_F was the mirror image of these two leads; in the precordial leads, a QS present from V_1 to V_5, a rS in V_6, and the T wave was inverted in V_1 to V_3, and upright in the left-sided chest leads.

In order to explain these findings, the zone of transition of upright to inverted QRS complexes (left and right ventricular potentials) was determined in various planes of the thorax. The distribution of these two contours over the thorax suggested that the unusual pattern in the conventional leads was due to an abnormal anatomical position of the heart, effected by marked clockwise rotation on the longitudinal and antero-posterior axes, with simultaneous backward rotation of the apex.

PICK

Carello, L.: Homogenicity of the Thoracic Electric Field and the Origin of the Spatial Vectorcardiogram. Acta cardiol. **7**: 117 (Fasc. 2), 1952.

The concept of vectorcardiography implies two basic assumptions, namely homogenicity of the thoracic electrical field and identity of the origin of the cardiac vector with the center of the heart. While the first assumption is supported by the possibility of finding mirror image potential on diametrically opposed positions of the chest, the second seems to be invalid, since intersections of the axes connecting mirror image potentials do not always traverse the center of the heart, determined radiologically. Studying this problem, the authors found that the electric center was located outside and dorsally to the heart shadow in 21 per cent of normal cases, in 60 per cent of cases with right ventricular hypertrophy and in almost 50 per cent of cases with left ventricu

lar hypertrophy or generalized cardiac enlargement. The greater incidence of these findings in pathologic hearts may be partly due to alterations in position, especially rotation of the heart in association with increase of its size.

PICK

Langendorf, R., Lev, M., and Pick, R.: Auricular Fibrillation with Anomalous A-V Excitation (W.P.W. Syndrome) Imitating Ventricular Paroxysmal Tachycardia. Acta cardiol. **7**, 241, 1952.

A case is reported of rheumatic mitral stenosis with Wolff-Parkinson-White syndrome, followed by flutter and fibrillation. Autopsy with incomplete microscopic study failed to reveal any accessory bundle on the right side. Two types of ventricular complexes were noted during auricular fibrillation; the wider complexes, similar to those recorded when the sinus rhythm was still present, are interpreted as caused by anomalous A-V excitation.

In cases with auricular fibrillation and abnormal excitation, the combined use of digitalis plus quinidine is recommended.

Considerations upon the mechanism of production of similar disturbances exclude the theory of an irritable focus but fail otherwise to clarify the obscure syndrome reported.

LUISADA

Dressler, W., Roesler, H., and Lackner, H.: The Significance of Notched, Upright T Waves. Brit. Heart J. **13**: 496, 1951.

Incidence and significance of notched, upright T waves are studied. They were observed in 16 per cent of the tracings from a series of 1000 electrocardiograms. While notched T waves were infrequently observed in the limb leads, and more frequently in the precordial leads, among normal subjects, they were frequently observed in the limb leads, and even more frequently in the precordial leads, of pathologic cases.

The significance of notched T waves is discussed. Notching of T is noticed under the same conditions which cause inversion of T; both notching and inversion of T can be observed simultaneously, and this is not unusual in impairment of the coronary blood flow.

The true notching of T should be differentiated from an apparent notching caused by fusion between U and T waves.

LUISADA

Ferrero, C., Doret, J., and Gay, E.: Contribution to the Diagnostic of Q_3, a Vectorgraphic Study. Cardiologia **20**: 47 (Fasc. 1), 1952.

A comparative study of 71 normal cases with a deep Q wave in lead III, and 40 cases showing this sign as consequence of myocardial infarction, revealed that currently used criteria for normal and abnormal Q waves, based on measurements of width and size of the deflection, are unreliable. About one half of the normal cases, and about one third of cases with proved myocardial infarction, were "exceptions to the rule." Association of Q_3 with a Q wave in lead II and aV_F, and its persistence in deep inspiration, proved more consistent with the diagnosis. This was especially brought out by vectorial analysis of the tracings. Vectors producing a deep Q_3 in normal persons are located in a mainly horizontal segment of the frontal plane and, hence, are most susceptible to respiratory variations. Contrary to this, a Q vector indicating posterior myocardial infarction is found in a more vertical segment of the frontal plane, and its position is much less variable with deep respiration.

PICK

Moll, A., and v. Lutterotti, M.: The Significance of the "Diskrepanz" Type of the R Wave ($r_I S_{II} S_{III}$ Pattern of the Electrocardiogram). Ztschr. Kreislaufforsch. **40**: 734 (Dec.), 1951.

The authors studied cases with the electrocardiographic syndrome of a small r in lead I and deep S waves in leads II and III. In the presence of this pattern, which was termed by others "discrepancy type," the possibility of an anterior wall infarct should always be considered, even when a distinct R wave is seen in lead II. In association with QRS prolongation, the pattern is frequently seen in the combination of anteroseptal infarction and right bundle branch block; the latter, however, can be recognized only in precordial leads, while the limb leads resemble more left bundle branch block. This apparent disagreement of limb leads and precordial leads is due to the change of the usual limb-lead pattern (namely, reduction of the prominent T wave in lead I) by ischemic myocardial destruction, rather than to an anomalous position of the heart. In rare occasions, the precordial leads indicate that the syndrome can occur in association with a left-sided conduction defect; and, sometimes, a completely atypical precordial pattern renders the localization of the intraventricular conduction defect to one or the other side extremely difficult or impossible.

PICK

Whitehorn, W. V., and Bean, J. W.: Cardiac Changes Induced by O_2 at High Pressure, High CO_2 and Low O_2, as Manifest by the Electrocardiogram. Am. J. Physiol. **168**: 528 (Feb.), 1952.

Decerebrate dogs were used. High oxygen (60 per cent) produced bradycardia and prolonged P-R interval which progressed to A-V block with longer exposures. P Waves were decreased or suppressed. Ventricular premature contractions and nodal rhythms were common with longer exposures. When the heart failed, the pacemaker and conduction were at fault. Vagotomy or vagotomy and stellatectomy increased the time required for the onset of findings but did not prevent them from appearing. High

carbon dioxide and low oxygen effects were very similar.

OPPENHEIMER

Moll, A., and v. Lutterotti, M.: An Evaluation of the "Diskrepanze" Type of the T wave in the Electrocardiogram. (The Pattern of $T_1 < T_3$.) Ztschr. Kreislaufforsch. **41:** 81 (Feb.), 1952.

The authors analyzed eight cases which, in the course of observation, showed the electrocardiographic syndrome of a small T wave in lead I associated with a tall T wave in III, and they arrived at the following conclusions:

The syndrome is suggestive but not diagnostic of coronary disease with infarction of the anterior wall. It is also found in incipient left ventricular hypertrophy, as a sign of digitalis effect, and in hearts with vertical position. If due to anterior wall infarction, it is usually associated with changes in the precordial leads and/or aV_L. The syndrome is seen commonly during the healing stages of anterior infarction and rarely in its initial stages, and seems to indicate a favorable prognosis. It develops sometimes in the course of transitory ischemia of the myocardium, without confluent infarction, and hence may be considered to be one of the manifestations of acute coronary insufficiency.

PICK

HYPERTENSION

London, F., and Perry, L. L.: The Soffer Test in Essential Hypertension. J. Clin. Investigation **31:** 51 (Jan.), 1952.

Subjects with Cushing's syndrome have an abnormal response to salt loading and the administration of desoxycorticosterone, in that they do not retain most of the salt following administration of this hormone.

Ten ambulatory male patients with essential hypertension were studied by means of this salt tolerance test. Nine of the ten patients showed a retention of chloride, and all ten showed a retention of sodium after salt loading and desoxycorticosterone acetate. Therefore, patients with essential hypertension did not show an electrolyte abnormality of the type found in patients with adrenal cortical hyperfunction (the Cushing syndrome).

WAIFE

Waldron, J. M., and Goldstein, F.: Changes in the Acid-Base Equilibrium in Essential Hypertension. J. Clin. Investigation **31:** 92 (Jan.), 1952.

The pH of a group of 19 patients with essential hypertension and normal kidney function was found to have a mean of 7.36, as compared to 14 normotensive subjects with a mean pH of 7.41. The increased acidity of the blood in hypertensives was accompanied by an increased carbon dioxide tension which averaged 47.4 mm. of Hg, compared to 39.6 mm. in normotensives. This is the pattern of primary respiratory acidosis. Hypertensives with impaired renal function showed a picture typical of metabolic acidosis with a low pH and a low carbon dioxide tension.

WAIFE

PATHOLOGIC PHYSIOLOGY

Kinmonth, J. B.: The Physiology and Relief of Traumatic Arterial Spasm. Brit. M. J. **4749:** 57 (Jan. 12), 1952.

The author discussed the causes of arterial spasm or other alterations in the size of large arteries, and means to combat this pathologic state. He found that direct stimulation of the femoral artery in the rabbit, using a faradic current, caused a contraction of the middle third of the vessel. Lumbar sympathetic stimulation produced a marked contraction of the distal third of the artery but not the upper third. With the intravenous injection of epinephrine, the lower part likewise became narrower, while the upper part actually dilated with the rise in blood pressure.

In man the author found that a similar state existed. Electrical stimulation of such vessels as the dorsal pedal artery caused contraction, while the same agent applied to the common femoral had no effect. On the other hand, the large vessels went into spasm when subjected to mechanical trauma. An intact sympathetic nerve supply was not necessary for the maintenance of this state, the local arterial spasm persisting for long periods after the sympathetic nerve supply had been removed from the vessels by periarterial sympathectomy.

Various procedures were tried to remove spasm. Intravenous administration of papaverine, caffeine, and priscoline was without effect on the spastic arteries, although each drug caused rapid relaxation when applied locally to the vessels. The direct use of benzodioxane produced partial relaxation, while inhalation of amyl nitrite had no effect. Of all the drugs tried, papaverine was the most consistently successful in eliciting permanent relaxation when applied locally. The spasm produced by mechanical trauma could not be relieved by sympathectomy.

It was concluded that in case of injury to an artery, early exploration is essential in order to distinguish between true spasm and compression of the vessel by bleeding. If spasm does exist, the entire segment of contracted artery should be exposed and then covered by a warm 2.5 per cent solution of papaverine sulfate and left for a few minutes. If relaxation does not occur within 10 to 15 minutes, the wound should be loosely closed, leaving a fine polyethylene tube in contact with the vessel for instillation of 1 per cent papaverine at intervals until the circulation is restored.

ABRAMSON

Angelino, P. F., and Actis-Dato, A.: Gas Analysis of the Renal Venous Blood and Renal Venous Pressures Studied by Means of Catheterization in Normal and Cardiac Patients. Cuore e circolaz. **35:** 283 (Oct.), 1951.

Catheterization of the renal veins was performed n 13 subjects. Three of them were normal subjects; hree had cardiac failure; two suffered from hyperhyroidism; while five suffered from various other ioncardiac ailments.

Renal venous pressure averaged 9 cm. water in iormal subjects, and 20 cm. water in heart failure.

Oxygen saturation averaged 90 per cent in normal subjects, 82 per cent in cardiac patients, and presented slight variations in other patients. Oxygen arteriovenous difference in renal blood was 1.23 per cent in normal subjects, while it was 4.22 in mixed blood. In cardiac failure, the A-V difference of the renal blood increased to 2.85 per cent; in the patients with hyperthyroidism, the difference was found low in the mixed blood.

The absorption coefficient of oxygen of the renal blood averaged 5.6 per cent, whereas it was 22 per cent in the systemic blood; the coefficient was higher in cardiac failure (average 10 per cent), corresponding to the increased value in the systemic blood. It was also higher in hyperthyroidism (9.5 per cent) and in patients with acute hepatitis.

The results of the study are correlated with the clinical findings.

LUISADA

Berthoud, E., and Zlotnick, A.: The Influence of Anoxemia on Cardiac Rhythm and Blood Pressure. Cardiologia **20:** 58 (Fasc. 1), 1952.

In a patient with partial respiratory paralysis, in consequence to poliomyelitis, discontinuation of artificial breathing resulted in bradycardia and elevation of the arterial pressure. The mechanism of these alterations was studied by recording continuous electrocardiograms and determinations of the oxygen and carbon dioxide saturation of the peripheral blood during a short period of depressed respiration. The experiments were performed with the patient breathing normal air and pure oxygen.

The study revealed that the blood pressure elevation was associated with the development of hyperkapnia, while slowing of the heart rate was related to hypoxemia. The mechanism of the bradycardia, as revealed by the electrocardiogram, consisted in the following sequence of events: First sinus bradycardia with successive displacement of the pacemaker towards the A-V node, and finally to a ventricular focus under disappearance of signs of sinus activity. With reoxygenation, restitution to normal rhythm took place in the reversed order. Thus, the cardiodynamics in asphyxia, studied for the first time in man, are similar to those observed by others in the animal experiment.

PICK

Longcope, W. T., and Freiman, D. G.: A Study of Sarcoidosis Based on a Combined Investigation of 160 Cases Including 30 Autopsies from the Johns Hopkins Hospital and Massachusetts General Hospital. Medicine **31:** 1 (Feb.), 1952.

The authors present a comprehensive review of sarcoidosis, particularly the pathologic and clinical features of this protean disease. Though involvement of lymph nodes, lungs, skin, spleen, liver, eyes and bones are well known, comparatively little attention has been paid to the cardiovascular damage resulting from direct myocardial involvement or from the effects of pulmonary sarcoidosis.

Cardiac involvement has been found in about 20 per cent of autopsies (including those reported in the literature). The lesions vary from scattered solitary tubercles in the myocardium to extensive infiltration of the muscle of both ventricles by great masses of sarcoid tissue. Death due to chronic heart failure or sudden death may occur in the cases with overwhelming infiltration. In the cases with minor degrees of involvement temporary disturbances may occur during the kaleidoscopic course of sarcoidosis. Various arrhythmias and tachycardias may accompany myocardial failure. Minor irregularities and electrocardiographic abnormalities without other cardiac symptoms are comparatively common.

A complication of severe pulmonary involvement is cor pulmonale. The latter may be quite severe in cases of infiltrating pulmonary sarcoidosis, in which a condition of "alveolar-capillary block" hastens the deterioration produced by the accompanying emphysema and the mechanical interference with blood flow through the small pulmonary vessels. Cardiorespiratory failure secondary to pulmonary hypertension and marked anoxia may terminate the life of many patients with pulmonary sarcoidosis. The characteristic features of this group of cases are dyspnea and cyanosis. It is to be hoped that continuation of current studies of the effect of adrenocorticotropic hormone and cortisone upon sarcoidosis may lead to a better understanding of the disease and better clinical results.

ENSELBERG

PATHOLOGY

Grewin, K. E.: Two Cases of Polypus Cordis. Cardiologia **20:** 40 (Fasc. 1), 1952.

The author presents clinical data of two instances of a large pedunculated myxomatous tumor of the left auricle, revealed by autopsy. Both cases showed during lifetime signs of chronic heart failure, one with unexplained attacks of suffocation, the other with sudden unexplained deterioration of the condition. This could have, according to the author, suggested the correct diagnosis. In view of the recently developed technics, surgical removal of tumors located in the left auricle appears possible. The literature was reviewed in order to establish criteria for intravitam diagnosis of the condition.

Signs which may arouse suspicion of the presence of a left auricular tumor are especially sudden appearance and disappearance of auscultatory signs of mitral stenosis, and attacks of syncope and unconsciousness, related to postural changes and not referable to heart block.

PICK

Klein, G.: A Case of Diffuse Endocardial Fibrosis in an Infant. Ztschr. Kreislaufforsch. **41:** 138 (Feb.), 1952.

A 5 weeks old female infant, dyspneic from birth, showed at examination enlargement of the heart to both sides and of the liver to the umbilicus. With improvement under treatment with digitalis, a systolic murmur appeared over the precordium. The child died on the thirty-ninth day of life with signs of bronchopneumonia. At autopsy, diffuse fibroelastosis of the endocardium was found, most marked in the left ventricle. The leaflets of the mitral valve were thickened and shortened, and its chordae tendineae were thickened and showed abnormal insertion, both resulting in severe stenosis of the mitral ostium. The aortic valves were hypoplastic, the left ventricle unusually small, the left auricle dilated, and both right auricle and ventricle dilated and hypertrophied. The coronary vessels were normal.

The author rejects fetal endocarditis as the cause of this deformation and favors the possibility of a primary malformation of the endocardium and valves, with secondary changes in the cardiac structures, due to alterations of the direction of blood flow through the heart.

PICK

Hall, G. F. M.: The Significance of Atheroma of the Renal Arteries in Kimmelstiel-Wilson's Syndrome. J. Path. & Bact. **64:** 103 (Jan.), 1952.

Two types of glomerular lesions occurring in diabetic glomerulosclerosis, the nodular lesion and the exudative lesion, are briefly described on the basis of the findings in a series of 135 diabetic patients. Postmortem findings in 8 cases of Kimmelstiel-Wilson's syndrome dying in uremia show gross atheroma with much narrowing of the renal arteries.

Atheromatous involvement of the large and small branches of the renal artery gave the kidney a characteristic macroscopic appearance. The histologic picture in all 8 cases showed ischemic obliteration of vast numbers of glomeruli. The pathogenesis of the massive obliteration of glomeruli is discussed, and it is concluded that obliteration results from atheromatous narrowing of the renal arteries superimposed on severe arteriolosclerosis.

BERNSTEIN

McKeown, F.: The Pathology of Pulmonary Heart Disease. Brit. Heart J. **14:** 25 (Jan.), 1952.

The author attempted to estimate the importance of lesions of the pulmonary vascular tree as a morphologic basis for right ventricular hypertrophy that was found in 111 instances of pulmonary heart disease in 6770 consecutive necropsies.

The cases were divided into three groups: Group I consisted of obstructive lesions of the pulmonary vascular system of which there were (a) four with pulmonary arteritis resembling periarteritis nodosa, (b) two with metastatic tumor, one of multiple embolization and the other of lymphangitis with reactive fibrosis that occluded vessels, (c) five with recurrent embolizations lasting from months to five years. Group II included five instances without morphologic lesions in the pulmonary vasculature or parenchyma, so-called primary pulmonary hypertension. Group III consisted of 39 with emphysema. Severe sclerosis was found in 17 per cent of these as compared to 10 per cent of emphysema without right ventricular hypertrophy and 7 per cent in controls.

The author concludes that the pulmonary vascular changes cannot be regarded as a morphologic basis of right ventricular hypertrophy. At the most, one may say that it accentuates slightly the normal age changes in the pulmonary vasculature.

SOLOFF

Heard, B. E.: An Experimental Study of Thickening of the Pulmonary Arteries of Rabbits Produced by the Organization of Fibrin. J. Path. & Bact. **64:** 13 (Jan.), 1952.

Large autogenous worm clots were converted into fibrous tissue in the pulmonary arteries of rabbits inside a month or six weeks. Small autogenous clots produced by intravenous magnesium adenosine triphosphate with Russell viper venom and by Harrison's technic appeared to leave the lungs within about two days. It is suggested that while small clots were destroyed by a fibrinolysin, large clots survived long enough to become organized and converted into fibrous tissue. The degree of intimal change in the pulmonary vessels visible after six weeks, however, was extremely slight. It is possible that fibrinolysis may be less efficient in the systemic arteries of human beings and may be reduced in activity by certain changes in the condition of the body over the long period of development of human atherosclerosis. This would allow thrombi to persist long enough to become organized and converted into fibrous thickening.

BERNSTEIN

PHARMACOLOGY

Roussak, N. J.: Fatal Hypokalemic Alkalosis with Tetany during Liquorice and P.A.S. Therapy. Brit. M. J., **4754:** 360 (Feb.), 1952.

This is a report on a patient who, while receiving treatment for tuberculous meningitis, developed unexplained electrolyte abnormalities from which she

died. The biochemical findings on the last two days of life were those of a hypochloremic hypokalemic alkalosis. There seems to be good circumstantial evidence that liquorice was responsible for the electrolyte changes shown by this case. It has been shown that liquorice has a desoxycortone-like action, and several other patients who received P.A.S. favored with liquorice developed tetany with hypokalemia. The P.A.S. could hardly have produced the observed electrolyte changes, because salicylate causes a respiratory alkalosis with low-alkali reserve, but the addition of a mild respiratory alkalosis to the metabolic alkalosis caused by the liquorice would favor the occurrence of tetany.

BERNSTEIN

Jayne, H. W., Scheinberg, P., Rich, M., and Belle, M. S.: The Effects of Intravenous Papaverine Hydrochloride on the Cerebral Circulation. J. Clin. Investigation **31:** 111 (Jan.), 1952.

A group of 18 subjects with various diseases was studied by the nitrous oxide technic. Cerebral circulatory studies were performed before and after the intravenous administration of papaverine hydrochloride in doses of 0.2 Gm. in 200 cc. normal saline over a 15 to 20 minute period. It was found that this drug led to a 13 per cent increase in cerebral blood flow, with a reduction in arterial-cerebral venous oxygen difference, so that cerebral oxygen consumption showed no significant change. There was a significant decrease in cerebral vascular resistance and fall in arterial pressure. There is suggestive evidence that papaverine probably causes arteriolar dilatation, although not localized to the brain.

WAIFE

Ransom, V. R., and Loomis, J. S.: The Effect of Ouabain on the Respiration of the Isometrically Contracting Rat Auricle. J. Pharmacol. & Exper. Therap. **104:** 219 (Feb.), 1952.

Ouabain was found to raise significantly the respiratory quotient of intact rat auricular tissue, mainly by increasing the production of carbon dioxide more than the oxygen uptake. At toxic levels the carbon dioxide production decreased from its maximum level at a faster rate than did oxygen consumption. The respiratory quotient of auricles contracting under tension was greater than when the tissue was not exposed to tension, since they were due to a higher rate of metabolism. Ouabain caused a biphasic response on respiration, depending upon its concentration. The increased respiratory phase of the ouabain effect did not result from an increased rate of contraction of the tissue. The authors believe that their results favor the theory that the cardiac glycosides stimulate the oxidative respiratory system of the myocardial cells by increasing the amount of endogenous metabolites consumed so that each contraction results in a greater increase in carbon dioxide production than it does in oxygen utilization.

SAGALL

Lequime, J., Courtoy, P., and Kenis, J.: Hemodynamic Alterations Following Administration of Procaine Amide to Normal Persons. Acta cardiol. **7:** 189 (Fasc. 2), 1952.

The effect of procaine amide upon the circulation was studied in normal persons, using cardiac catheterization. The drug was injected in doses of 500 to 800 mg., either intravenously or directly through the catheter into the right ventricular cavity. In six out of seven experiments, the arterial pressure dropped within 10 minutes following the injection, the systolic pressure maximally by 40 mm. and the diastolic by 20 mm. Cardiac output and the cardiac index increased in all instances. With exception of a slight prolongation of the P-R interval and of the QRS duration, no changes were observed in the electrocardiogram.

The authors ascribe the observed changes of the hemodynamics to a twofold action of procaine amide upon the circulation, consisting in peripheral vasodilatation and a depressant action upon the myocardium. While the former action dominates in normal subjects, myocardial depression becomes manifest in diseased hearts. This may explain some apparent disagreement of the results of the present study with those reported by others in subjects with cardiac pathology. In view of these observations, intravenous administration of procaine amide requires caution and should be used only with strict indications.

PICK

Frank, H. A., Jacob, S. W., Schweinburg, F. B., Goddard, J., and Fine, J.: Traumatic Shock. XXI. Effectiveness of an Antibiotic in Experimental Hemorrhagic Shock. Am. J. Physiol. **168:** 430 (Feb.), 1952.

In control experiments 88 per cent of dogs died of hemorrhagic shock. If animals were given aureomycin hydrochloride until two successive stool cultures were free of *Escherichia coli* and clostridia (10 to 12 days) 88 per cent survived. It was later discovered that six days of pretreatment (2.5 Gm. twice daily) was adequate, whether or not stool cultures were free of the two organisms mentioned at this time. The authors conclude that bacterial action facilitates the development of irreversibility to transfusion in hemorrhagic shock.

OPPENHEIMER

Yonkman, F. F., Plummer, A. J., and Reitze, W. B.: Suppression of Tachycardia Induced By 2-N-P-Tolyl - N (M′-Hycroxyphenyl) - Aminomethyl - Imidazoline (Regitine) C-7337. Arch. internat. pharmacodyn. **89:** (Jan.), 1952.

The ganglionic blocking agents, pentamethyl-diethyl-3-azapentane-1,5-diammonium-dibromide (C-9295) (Pendiomide), tris-(2-diethyl-aminoethyl)-amine trihydrochloride (Su-1194), hexamethonium (C_6) and tetraethylammonium chloride (Etamon), as well as Veratramine and tincture of Veratrum viride, antagonized the tachycardia produced by Regitine in 60 experiments on dogs under sodium pentobarbital anesthesia.

BERNSTEIN

Randall, B. F., Imig, C. J., and Hines, H. M.: Effects of Some Physical Therapies on Blood Flow. Arch. Phys. Med. **33:** 73 (Feb.), 1952.

The effect of several physical therapies on the volume blood flow through the hind extremities was studied on a series of unanesthetized adult dogs. Massage produced little increase in local circulation, while passive stretching caused a significant augmentation in normally innervated and spastic limbs but not in those that were denervated. Electrical stimulation of muscle was followed by a definite increase in blood flow, although during the actual period of tetanic contraction there was a decrease. The consecutive application of three hot packs caused an augmentation in the normally innervated limb but no change when the skin was previously treated with Butesin.

The question was raised as to whether the increase in blood flow following application of heat and exercise was worthwhile, since there was a simultaneous rise in the metabolic needs of the affected tissues.

ABRAMSON

Cole, F.: Cardiac Massage in the Treatment of Arrest of the Heart. A Study of Three Hundred and Fifty Cases with Two Original Case Reports. Arch. Surg. **64:** 175 (Feb.), 1952.

To the series of 348 cases of arrest of the heart reported in the literature, the author added two of his own. Of this number recovery occurred in 112. In those instances in which cardiac massage was carried out, 110 of 212 lived. Only three of the patients who recovered showed residual effects.

It was concluded that cardiac massage is the procedure of choice and that this should be instituted within five minutes after arrest has occurred and not when all other measures have failed.

ABRAMSON

PHYSICAL SIGNS

Fassbender, H. G., and Wengler, G.: Etiology of Subendocardial Bleeding. Virchow's Arch. path. Anat. **321:** 138 (Fasc. 2), 1952.

In 32 necropsied cases with subendocardial hemorrhage located mainly in the outflow tract of the left ventricle, a study of clinical data revealed signs of vagal stimulation as a common denominator. Thus, in one group of patients there was evidence of increased intracranial pressure, and in another group enlargement of cervical nodes was found in proximity to the vagus nerve. One case died a "bolus death" after an attempt to swallow a big piece of sausage, and another shortly after a thyroid operation from bleeding into the mediastinum. Among other possible explanations the authors consider "nervous disturbances of the terminal vascular bed" as most likely cause of the bleeding in this particular localization.

PICK

Luisada, A. A.: The Diastolic Sounds of the Heart in Normal and Pathological Conditions. Acta med. Scandinav. (Suppl. 266) **142:** 685, 1952.

A review of the various cardiac sounds (or tones) is made. It is suggested that the two most common sounds be called *first* and *second sound complex* and that both be classified as *systolic sounds*. The *third* and *fourth* (*auricular*) *sound* should be called *diastolic sounds*. A systematic study of the diastolic sounds was made. In about *eight per cent* of the cases, additional vibrations were found following the diastolic sounds; these were in early diastole, presystole, or both.

The cases having additional vibrations were broken down by age groups and by etiologic groups: (a) The early diastolic vibrations were more frequent between 10 and 29; they were present in some normal adolescents but were more frequent in various types of heart disease. (b) The presystolic vibrations were more frequent between 10 and 19, and again in the old-age groups; they were found only in heart disease.

The various factors responsible for the diastolic sounds in general and for the additional vibrations in particular are discussed. It is postulated that, in the majority of cases, a slightly asynchronous rapid passive filling of the ventricles is responsible for the double third sound; a slightly asynchronous contraction of the auricles, for the double fourth (auricular) sound.

Knowledge of these possible additional sounds is essential for the exact interpretation of diastolic vibrations in the phonocardiograms and the differential diagnosis between mitral stenosis and other types of heart disease.

LUISADA

PHYSIOLOGY

Luisada, A. A., Alimurung, M. M., and Lewis, L.: Mechanism of Production of the First Heart Sound. Am. J. Physiol. **168:** 226 (Jan.), 1952.

A series of *open-chest experiments* was made in order to study the mechanism of production of the first heart sound under the following conditions: (a) in the empty heart; (b) after ligation of the A-V groove; (c) after extensive damage of the A-V valves; (d) after the ligation of the large arteries and (e) after necrosis of the ventricular walls.

Phonocardiograms were recorded together with tracings of either the cardiac volume or the left ventricular pressure. The experiments did not allow the separation of the vibrations arising in the valves from those arising in the cardiac muscle, since it was impossible to alter ventricular pressure without changing the force of closure of the A-V valves, or to damage the A-V valves without altering ventricular pressure.

Studies were performed on *normal human subjects* by recording the low-frequency (apical cardiograms) and the high-frequency vibrations (phonocardiograms) of the chest wall, and on *normal dogs and rabbits* by recording left ventricular pressure and phonocardiograms. They confirmed the existence of two groups of vibrations within the first sound. These two groups of vibrations coincide with the two main valvular events of early systole (closing of the A-V valves and opening of the semilunar valves) and with two distinct waves in the low-frequency tracing of the chest (apex cardiogram).

It is suggested that the first sound is the result of a combination of muscular and valvular factors. Sudden changes in muscular tension activate first the A-V valves and then the semilunar valves. This rapid succession causes a double vibration of the cardiac wall and is further transmitted to the chest wall, including high-pitched (sound tracing) and low-pitched (cardiogram) components. Although simultaneous with the action of the valves, these vibrations are likely to arise in both the valvular and the muscular structures as a response to rapid changes in tension and pressure. Smaller vibrations, possibly of muscular origin, may be seen at times between the two main groups of vibrations of the first sound. Vascular vibrations occur only later, after the beginning of ejection, and have a lower pitch and lesser amplitude.

LUISADA

Fowler, N. O., Jr., Westcott, R. N., and Scott, R. C.: Pulmonary Artery Diastolic Pressure: Its Relationship to Pulmonary Arteriolar Resistance and Pulmonary "Capillary" Pressure. J. Clin. Investigation **31**: 72 (Jan.), 1952.

In the systemic circulation there is an increased peripheral resistance when the diastolic pressure is elevated. This is a report on a study of such relationships within the pulmonary circulation. Catheterization of the heart and determination of cardiac outputs by the direct Fick method were performed in a group of 54 patients with miscellaneous heart and lung diseases. A significant correlation was found between the pulmonary arteriolar resistance and the systolic, diastolic, and mean pulmonary artery pressure. However, the correlation of arteriolar resistance with diastolic pressure was no closer than with the mean or systolic pressures. It would appear that a rise in pulmonary arteriolar resistance increases the pulmonary artery pressure, and this increase is as great or greater in the mean or systolic pressures than in the diastolic.

There was a significant negative correlation between arteriolar resistance and arterial oxygen saturation. The pulmonary "capillary" pressure was significantly correlated with the pulmonary artery diastolic pressure.

The authors conclude that there was no evidence that an increased arteriolar resistance produced a disproportionate elevation in pulmonary diastolic pressure as compared to mean or systolic pressures.

WAIFE

RHEUMATIC FEVER

Long, D. A.: Cortisone, Allergy, and Rheumatic Fever. Ann. Rheumat. Dis. **10**: 427 (Dec.), 1951.

The author hypothecates, based on guinea-pig experiments, that the oxidation of ascorbic acid is associated with desensitization and that cabbage contains an — SH compound which prevents oxidation. Cortisone antagonizes this cabbage effect and permits ascorbic-acid oxidation to occur once more.

From these hypotheses, he argues that dehydroascorbic acid should prove clinically effective in man in the treatment of rheumatic fever. He warns that this substance resembles alloxan chemically and may be diabetogenic. Only further work will prove these hypotheses.

BERNSTEIN

Salazar Mallen, M., and Castillo, F.: Studies on Genetics of Rheumatic Fever. 1. The hypothesis of a Rheumatic Gene. Arch. Inst. cardiol. Mexico. **22**: 136, 1952.

The authors studied 40 rheumatic families in order to investigate the possible importance of heredity in rheumatic fever. The results of this study seem to confirm Wilson's conclusions. According to the authors, transmission of a rheumatic heredity by a recessive gene should be considered as proved.

LUISADA

ROENTGENOLOGY

Porte, D.: Detection of Heart Disease in a Mass Chest X-ray Survey for Tuberculosis Case-finding. Ann. Int. Med. **36**: 603 (Feb.), 1952.

In this study, the roentgenograms of the chest of 6,579 persons over 15 years of age, made in mobile units using 70 mm. film, were examined with a view to determining the incidence of an abnormal cardiac shadow and correlating this finding with other methods of examination of the cardiovascular system. Thus, an abnormality of the heart was noted in 87 of the roentgenograms. Subsequent examinations of the 87 persons indicated that 19 had heart disease which was previously unknown, 26 had cardiovascular disease which was previously known, and 25 were found to be free of organic heart disease. Most

of the cases of rheumatic disease were previously known, whereas more than half the cases of hypertensive arteriosclerotic heart disease were discovered for the first time through the chest roentgen-ray survey. These findings compare favorably with the productivity of the survey from the point of view of tuberculosis case-finding.

WENDKOS

Smith, P. G., Evans, A. T., Elsey, E. C., and Felson, B.: Translumbar Arteriography: Its Roentgenologic Interpretation. Am. J. Roentgenol. **67**: 183 (Feb.), 1952.

The authors discuss the findings and applications of translumbar arteriography performed in more than 300 instances. The technic of the procedure is briefly described and the normal arteriogram described and illustrated. The findings in renal anomalies, cysts and tumors of the kidney, other abdominal tumors, hydronephrosis, pyelonephritis, arterial aneurysm and thrombosis, and pregnancy are given, and the value of the method in each of these conditions is discussed.

The amount of circulation in the kidneys can readily be estimated, permitting pertinent deduction as to whether the affected kidney need be removed. Among many patients studied for possible renal origin of hypertension, no instance of the Goldblatt kidney was encountered, though the authors cite a reference in which obstruction of the main renal artery with demonstrable collateral circulation was shown in a patient with hypertension, and this was believed to be cause and effect. The diagnosis of renal infarction was made in four instances and proved at operation in one and by autopsy in the other three. Abdominal aortic aneurysm and splenic artery aneurysm were each demonstrated once; abdominal aortic thrombosis occurred in one instance.

The authors conclude that translumbar aortography is a relatively simple and safe procedure, and that it offers valuable information not obtainable by any other means.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Ravitch, M. M.: Unusual Sternal Deformity with Cardiac Symptoms—Operative Correction. J. Thoracic Surg. **23**: 138 (Feb.), 1952.

A sternal deformity is described in which the depressed body of the sternum displaced the heart to the left, producing symptoms. The angulation of the sternum was a double one, with an anterior bowing in the superior portion, in addition to the usual concavity inferiorly. The complaints consisted of attacks of palpitation followed by slowing of the heart and heavy breathing.

Resection of small segments of five costal cartilages on each side, division of the xiphisternal joint, and transverse osteotomies of the sternum at each of the levels of angulation relieved the symptoms.

ABRAMSON

Spencer, F. C., Muller, W. H., Jr., and Longmire, W. P., Jr.: Experimental Pulmonic Valvulotomy under Direct Vision by Temporarily Occluding the Pulmonary Artery. Ann. Surg. **135**: 34 (Jan.), 1952.

A method is described of occluding the pulmonary circulation in dogs so as to permit the performance of pulmonary valvulotomy under direct vision. The pulmonary artery and right ventricular outflow tract were closed off with clamps, and a longitudinal incision was made in the pulmonary artery. The valve cusps were then cut through the opening, using a bayonet forceps. A Potts ductus clamp was applied to the incision in the pulmonary artery and the two occluding clamps were removed. Following this the incision was closed with a double row of sutures. Of the 10 dogs operated on in this manner, eight survived. It was believed that the maximum time that the circulation could be arrested without causing death was between three and one-half and five minutes. The clinical implications of such an operation were discussed.

ABRAMSON

Lam, C. R., Aram, H. H., and Munnell, E. R.: An Experimental Study of Aortic Valve Homografts, Surg., Gynec. & Obst. **94**: 129 (Feb.), 1952.

An experimental study in which valve-bearing segments of a dog's aorta were grafted to recipient dogs was undertaken. Since plastic valvular prostheses had been unsatisfactory, the authors felt that aortic valve homografts might be more successful.

Valve-bearing segments of aorta were implanted in the thoracic aorta of recipient dogs. The circulation in the distal aorta was interrupted no more than five minutes, and paralysis of the hind limb did not result. Care was taken to be sure that the valve segment had the correct relationship to the direction of blood flow. This was performed in 27 dogs, and seven of these animals survived from one to six months, at which time they were sacrificed.

Inspection of the valves in the animals which died early revealed that they were capable of function and were competent when water was injected in a retrograde fashion against them. Valves that were in place for longer periods were shriveled and thrombosed and were not functional. In segments which had been implanted for 12 months, no valve cusp was identifiable. The authors concluded that this method of valve grafting offered no promise of success as far as function was concerned.

The problem was then approached by studying the effect of a need for function on the survival of these valve homografts. Aortic insufficiency was produced in dogs by incising the posterior aortic cusp with a transventricular valvulotome. Then

valve-bearing segments of aorta were grafted into the thoracic aorta of these dogs. A total of 18 of these dogs survived for study. Early after surgery study by intra-arterial pressure readings revealed that the natural aortic valves were incompetent while the grafted valves were competent and functional. Interim studies revealed that the grafted valves continued to function in only two animals. At autopsy the transplanted valves appeared almost normal and capable of function in one half of the animals. However physiologic investigation had shown that none of these valves was functioning. Autopsy also revealed a tendency toward spontaneous correction of the aortic valvular insufficiency that had been induced by the valvulotomy. This correction was usually by adaptation of the other two leaflets over the defect. This phenomenon prevented definite conclusions as to the fate of an aortic valve homograft in the presence of a persistent aortic insufficiency in the host.

It is possible to transplant an aortic valve homograft into the thoracic aorta of a recipient animal, and one might speculate that it would retain its functional capacity if the host animal had marked permanent aortic insufficiency.

FROBESE

THROMBOEMBOLIC PHENOMENA

Anlyan, W. G., Campbell, F. H., Shingleton, W. W., and Gardner, C. E., Jr.: Pulmonary Embolism Following Venous Ligation. Arch. Surg. **64:** 200 (Feb.), 1952.

The authors found that during a 12-month period, 50 instances of thromboembolic disease occurred on the surgical and gynecologic services of a large general hospital. Of these 43 were treated with anticoagulants only, and seven by venous ligations, five of the latter also receiving anticoagulants.

Of the seven patients who were treated surgically, in four bilateral superficial femoral vein ligation was performed just distal to the deep femoral branch. Three of these subsequently developed pulmonary emboli, with one death. Two cases in this group were also treated with anticoagulants and recovered. Two patients were subjected to bilateral common femoral and saphenous vein ligations. One of these had an uneventful course, while the other developed a pulmonary embolism which was treated with anticoagulants. The last patient in the series had a bilateral popliteal vein ligation for deep venous insufficiency and subsequently developed a pulmonary embolus. He also received dicumarol and recovered.

It was concluded that it is questionable as to whether there is any indication for ligation of the superficial femoral or common femoral veins in thromboembolic disease. Furthermore, once these procedures have been performed, there is no justification for a feeling of security from fatal pulmonary embolism. Anticoagulant therapy appears to be the treatment of choice in the prevention of pulmonary embolism.

ABRAMSON

Aguiar, J. A., Schlesinger, P., and Barretto Netto, M.: Coronary Embolism due to Pre-existent Thrombosis. Arq. brasil med. **42:** 21 (Jan.–Feb.), 1952.

A case is reported of a 41 year old male with arteriosclerotic and hypertensive heart disease whose initial electrocardiogram showed no evidence of myocardial infarction. Following an acute episode of precordial pain, the tracing revealed typical changes of recent anterior and posterior infarction. The patient died soon after this record was obtained. Autopsy revealed multiple coronary embolization originating in a pre-existent partially occluding thrombus of the main branch of the left coronary artery.

SCHLESINGER

Ellis, J. T., and Windham, S. W.: Acute Massive Venous Occlusion in the Lower Extremity. Ann. Surg. **135:** 262 (Feb.), 1952.

Two cases are reported of acute massive venous occlusion in the lower extremity. The clinical manifestations of this condition consist of a rapid onset of severe pain in the inguinal region and upper portion of the leg, extending downward into the leg, associated with the appearance of a marked degree of pitting edema of the entire lower extremity up to the groin. These changes are followed by blue discoloration which begins in the foot and leg and then gradually proceeds upward onto the thigh. Arterial pulsation may or may not be present in the involved limb. The process may progress to gangrene depending upon the amount of venous involvement. This change results from circulatory arrest caused by blockage of the venous return from the extremity. Arterial blood cannot reach the tissues due to the extreme venous pressure built up in the involved extremity by the extensive venous occlusion.

The treatment of the condition consists of the sucking out of the clots from the major venous channels of the thigh. Sympathetic blocks do not alleviate or correct the clinical manifestations.

ABRAMSON

VASCULAR DISEASE

Elliott, R. V., and Peck, M. E.: Thrombotic Occlusion of Aorta as Demonstrated by Translumbar Aortograms. J. A. M. A. **148:** 426 (Feb. 9), 1952.

The authors describe the technic for translumbar aortographic examination and state it can be performed without great risk to the patient. They report in detail four cases which were studied by this technic and diagnosed as thrombotic occlusion of the aorta. The value of making an accurate diagnosis in occlusion of the aorta is extremely important

to the welfare of the patient because it affects the therapy which is instituted. A positive diagnosis between coarctation of the aorta, abdominal aneurysm, and thrombotic obliteration of the aorta can be established by translumbar aortographic examination. In addition the exact location of the lesion can be identified. This procedure does not carry any undue risk when used in patients with aortic disease.

KITCHELL

Dunlop, G. R.: Problems of Ischemia of the Lower Extremity. New England J. Med. **246:** 219 (Feb. 7), 1952.

The author discusses the indications and contraindications for the use of lumbar sympathectomy in the treatment of ischemia of the lower extremities. Necrosis proximal to the toes, extensive visceral disease, advanced atrophy of the skin and subcutaneous tissue, and severe rest pain negate the use of such a procedure, since these conditions represent advanced states of the occlusive arterial disorder. Peripheral ischemia associated with a cold moist foot, intermittent claudication with palpable popliteal pulses, superficial necrosis of the toes with demonstrable vasospasm, and peripheral ischemia that responds to a sympathetic block are states in which sympathectomy is indicated.

ABRAMSON

Charbon, B. C., Adams, W. E., and Carlson, R. F.: Surgical Treatment of Multiple Arteriovenous Fistulas in the Right Lung in a Patient Having Undergone a Left Pneumonectomy Seven Years Earlier for the Same Disease. J. Thoracic Surg. **23:** 188 (Feb.), 1952.

A case of multiple arteriovenous fistulas of the right lung is reported. The diagnosis was first made in 1943 at which time the patient, a 24 year old male, was experiencing frequent nosebleeds. Cyanosis and clubbing of the fingers were present, while roentgenograms of the chest showed two lobulated opaque areas, one in each lung field. A left pneumonectomy was performed and the patient's condition improved.

In 1949 fluoroscopy revealed a new lesion in the lower right lung field, associated with the return of symptoms. The patient was again operated upon, and three separate arteriovenous fistulas were found in the right lung. Parts of the right lung were resected. The patient was discharged from the hospital in fairly good condition after a stormy postoperative course.

ABRAMSON

Ruggiero, G., and Castellano, F.: Carotid-Cavernous Aneurysm. Acta radiol. **37:** 121 (Feb.), 1952.

The authors discuss the clinical, diagnostic and therapeutic aspects in 11 patients with arteriovenous fistulas between the internal carotid artery and the cavernous sinus. In the seven cases due to trauma, the onset of symptoms was insidious with unilateral pulsating exophthalmos, involvement of the second, third, fourth or sixth cranial nerves, and intracranial bruit. Chemosis and subcutaneous hemorrhages were common. In the four cases with spontaneous fistula formation, the onset was acute with headache, vomiting, and bruit, while the exophthalmos generally appeared later.

Arteriography in the postero-anterior and lateral views was considered essential. Treatment was more satisfactory in the traumatic group. One case responded to daily digital compression of the common carotid artery; the others required ligation of the common carotid artery, the internal carotid artery, the intracranial portion of the internal carotid or a combination of two or all of these procedures.

The authors believe that the collateral supply comes from the opposite common carotid artery rather than from homolateral external carotid branches.

SCHWEDEL

OTHER SUBJECTS

Downey, V. M., and Strickland, B. A.: Air Transportation of Cardiac and Pulmonary Patients. Ann. Int. Med. **36:** 525 (Feb.), 1952.

The important consideration in flight is the oxygen supply of the myocardium which depends upon the coronary circulation and upon the oxygen saturation of the blood. Above 15,000 feet, oxygen saturation falls off rapidly, so that no amount of coronary dilatation could provide a sufficient oxygen supply for the myocardium. Therefore, above 10,000 feet, additional oxygen must be available for any person with heart disease. Whether an individual patient should be transported by air or not depends upon his condition, the altitude to be flown, the availability of oxygen, and the qualifications of the flight attendant. In general, however, a patient who can be transported at all can be flown below 10,000 feet, since oxygen saturation of blood remains satisfactory below this level and since experience indicates that patients with coronary deficits, valvular heart disease, and cardiac arrhythmias will tolerate flights made below 10,000 feet without the development of symptoms referable to the heart.

WENDKOS

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FIRST ISSUE OF "CIRCULATION RESEARCH"

The first issue of the new bimonthly Journal, Circulation Research, will appear in January. The only journal of its kind, Circulation Research will fill the need for a scientific medium reporting on fundamental investigations related to the heart and circulation.

Edited by Dr. Carl J. Wiggers, Circulation Research aims to narrow the gap between the completion of a discovery and its final publication, by offering regular, up-to-date and correlative coverage of important basic research.

The departments to be found regularly in Circulation Research will include original research articles, editorials on pertinent and timely subjects, and a section on "Research in Progress" covering preliminary reports of advances in current research.

The January issue will include the following papers:

Ferguson, T. B., O. W. Shadle and D. E. Gregg: Effect of Blood and Saline on Ventricular End Diastolic Pressure, Stroke Work, Stroke Volume and Cardiac Output in the Open and Closed Chest Dog.

Ferrer, M. I., R. M. Harvey, M. Kuschner, D. W. Richards, Jr., and A. Cournand: Hemodynamic Studies in Tricuspid Stenosis of Rheumatic Origin.

Gaskell, P. and A. C. Burton: Local Postural Vasomotor Reflexes Arising from the Limb Veins.

Harris, A. S., R. W. Olsen, A. Estandia and T. J. Ford, Jr.: Oxygen Administration upon Ventricular Tachycardia and Blood Pressure in Animals with Acute Myocardial Infarction.

Heymans, C., A. L. Delaunois and G. van den Heuvel-Heymans: Tension and Distensibility of Carotid Sinus Wall, Pressoceptors and Blood Pressure Regulation.

Khairallah, P. A. and W. F. H. M. Mommaerts: Nucleutide Metabolism in Cardiac Activity. I. Methods and Initial Observations. II. Reactions in Systole.

Lanier, J. T., H. D. Green, J. Hardaway, H. D. Johnson and W. B. Donald: Basic Differences between Reactions of Cutaneous and Muscular Vessels to Adrenergic Drugs, Ischemia, Methacholine and Adrenergic Drugs Following Antiadrenergic Drugs.

Opdyke, D. F. and M. E. Zanetti: Extent of Agreement between Two Methods for Estimating Acute Directional Changes of Cardiac Stroke Index.

Randall, W. C., W. F. Alexander, J. W. Cox and A. B. Hertzman: Functional Analysis of the Vasomotor Innervation of the Dog's Hind Footpad.

NEXT INTER-AMERICAN CARDIOLOGICAL CONGRESS

The Fifth Inter-American Cardiological Congress will be held in Havana, Cuba, in 1956, it was decided at a meeting of the Inter-American Cardiological Society last September. The meeting was held in connection with the Fourth Inter - American Cardiological Congress in Buenos Aires. Co-chairing the Society's meeting were its permanent honorary Presidents, Drs. Ignacio Chavez of Mexico, and Dr. Louis N. Katz, Chairman of the American Heart Association's Scientific Council.

Dr. Pedro Cossio, of Argentina, was elected President of the Society for the next four years. On recommendation of the Committee on International Affairs of the American Heart Association, Howard B. Sprague, M.D., Boston, was elected a Vice-President of the Society; Teofilo Ortiz Ramirez, M.D., Mexico, was named Secretary; and George R. Herrmann, M.D., Galveston, Texas, was chosen an Assistant Secretary. Also on recommendation of the Association's Committee on International Affairs, the following Anglo-American members were elected to the Society's Board of Directors: Dr. Sprague; Carl J. Wiggers, M.D., Cleveland; Irving S. Wright, M.D., New York (continuing in office were John Hepburn, M.D., Toronto;

Dr. Herrmann; and Arlie R. Barnes, M.D., Rochester, Minn.).

PROGRAM OF THE SECTION ON CIRCULATION

Dr. Fay LeFevre, Chairman of the Section on Circulation, states that papers for the annual meeting of the Section on Circulation may be submitted to the Program Committee by any member of the American Heart Association. Dr. LeFevre says, "In the past, there has apparently been some misunderstanding and the Committee wishes to inform the membership that the program is not restricted to members of the Section on Circulation. Anyone interested in submitting a paper should forward to the Chairman a short summary in triplicate as soon as possible."

NEW BOOKLETS

Three booklets related to the employment of cardiacs are being distributed by the American Heart Association and its affiliates to assist the private and industrial physician in restoring their cardiac patients to gainful employmer wherever possible.

A medical guide, "Returning Cardiacs to Work," is intended specifically for the use of the physician in evaluating the physical capacity and the occupational possibilities of his cardiac patients. The manual also includes a list of official, voluntary and private agencies for the referral of patients by the physician for vocational counselling or retraining. The guide, written by the medical staff of the Bellevue Hospital Work Classification Unit, is based on experience gathered in ten years of operation of the unit, which was initiated by the New York Heart Association.

"Facts About Employment and Heart Disease," the second booklet in the group, is aimed directly at the cardiac worker, and is useful for distribution by the physician to his patients. This booklet was written in question and answer form by Dr. Leonard Goldwater, Chairman of the Association's Cardiac-in-Industry Committee.

For industrial physicians and management, the third booklet, "These Hands Are Able," was developed by the American Heart Association from a manuscript prepared by the Cardiac-in-Industry Committee of the Los Angeles County Heart Association.

All three booklets may be obtained through heart association affiliates or from the National Office.

REMINDERS

New Feature

The first section on Conferences, a new feature to be published six times annually in CIRCULATION, will appear in the next issue. Edited by Edgar V. Allen, M.D., and J. Earl Estes, M.D., the new section will cover clinical and clinicopathologic conferences on specific subjects.

Papers for the Scientific Sessions

January 1, 1953 is the last day on which those desiring to present papers at the Association's Scientific Sessions may submit abstracts. The abstracts should not be longer than 300 words and must contain in summary form, a specific statement of the results obtained or conclusions reached (not merely a statement that results or conclusions will be presented or discussed at the meeting). Abstracts should be submitted in *triplicate* to Dr. André Cournand, Chairman of the Program Committee, c/o American Heart Association, 44 East 23rd Street, New York 10, N. Y.

CALENDAR

Dec. 2–5: Sixth Annual Clinical Session of American Medical Association, Denver, Colo. (Will feature review lectures and panels on current progress in cardiovascular diseases.)

Apr. 8–12: **Twenty-Ninth Annual Meeting, American Heart Association, Hotel Chelsea, Atlantic City, N. J.**

Apr. 8–9: Assembly panels, Assembly meeting, meeting of Scientific Council.

Apr. 10–12: **Twenty-Sixth Scientific Sessions, American Heart Association, Hotel Chelsea, Atlantic City, N. J.**